THE UNIVERSITY *of* EDINBURGH

A Systematic Review and Meta-analysis of Transgenic Mouse Models of Alzheimer's Disease

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Wee, sleekit, cowran, tim'rous beastie,
O, what a panic's in thy breastie!
Thou need na start awa sae hasty,
Wi' bickering brattle!
I wad be laith to rin an' chase thee,
Wi' murd'ring pattle!
I'm truly sorry Man's dominion
Has broken Nature's social union,
An' justifies that ill opinion,
Which makes thee startle,
At me, thy poor, earth-born companion,
An' fellow-mortal!
I doubt na, whyles, but thou may thieve;
What then? poor beastie, thou maun live!
A daimen-icker in a thrave 'S a sma' request:
I'll get a blessin wi' the lave,
An' never miss't!
Thy wee-bit housie, too, in ruin!
It's silly wa's the win's are strewin!
An' naething, now, to big a new ane,
O' foggage green!
An' bleak December's winds ensuin,
Baith snell an' keen!
Thou saw the fields laid bare an' wast,
An' weary Winter comin fast,
An' cozie here, beneath the blast,
Thou thought to dwell,
Till crash! the cruel coulter past
Out thro' thy cell.
That wee-bit heap o' leaves an' stibble,
Has cost thee monie a weary nibble!
Now thou's turn'd out, for a' thy trouble,
But house or hald.
To thole the Winter's sleety dribble,
An' cranreuch cauld!
But Mousie, thou are no thy-lane,
In proving foresight may be vain:
The best laid schemes o' Mice an' Men,
Gang aft agley,
An' lea'e us nought but grief an' pain,
For promis'd joy!
Still, thou art blest, compar'd wi' me!
The present only toucheth thee:
But Och! I backward cast my e'e,
On prospects drear!
An' forward, tho' I canna see,
I guess an' fear!

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Declaration

I declare that this thesis represents my own work unless otherwise stated and has not been submitted for any other degree or professional qualification.

More specifically, the original systematic search was conducted by me under the guidance of Professor Malcolm Macleod (MM) and Dr Emily Sena (ES). For the systematic search results MM and I independently screened the results according to the inclusion criteria which were predefined. Within identified publications, all the data was extracted by me and meta-analysis was conducted by me under the supervision and support of the CAMARADES group as a whole. The writing of this thesis was by me, with guidance and advice from the CAMARADES group.

Thus this thesis is a representation of my own work throughout the course of the degree undertaken.

Kieren Egan 04/02/2013

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The patience, care and support of my friends, colleagues and family will not be forgotten. Collectively, it is to these people I am indebted.

Publications and Conference Participation

Publications

(1)Rooke EDM, Vesterinen HM, Sena ES,**Egan K**, Macleod MR. Dopamine agonists in animal models of Parkinson's disease: A systematic review and meta-analysis. Parkinsonism & Related Disorders 2011 Jun;17(5):313-20.

(2)**Egan K**, Sena E, Vesterinen H, Macleod M. Making the most of animal data - improving the prospect of success in pragmatic trials in the neurosciences. Trials 2011;12(Suppl 1):A102.

(3) Lees JS, Sena ES,**Egan KJ**, Antonic A, Koblar SA, Howells DW, et al. Stem cell-based therapy for experimental stroke: A systematic review and meta-analysis. Int J Stroke 2012 Jun 12.

(4) Vesterinen HV,**Egan K**, Deister A, Schlattmann P, Macleod MR, Dirnagl U. Systematic survey of the design, statistical analysis, and reporting of studies published in the 2008 volume of the Journal of Cerebral Blood Flow and Metabolism. J Cereb Blood Flow Metab 2011 Apr;31(4):1064-72.

Presentations and awards

Egan K, Sena E, Vesterinen H, Macleod M (2012) What have I learnt from testing interventions tested in transgenic mouse models in Alzheimer's disease that could help clinical trial design? MRC Trials Methodology Hub Student Symposium Bristol, (Platform presentation).

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Egan K, Sena E, Vesterinen H, Macleod M (2012) Understanding relationships between outcomes in Alzheimer's disease: a systematic review and meta-analysis of transgenic mouse models Federation of European Neurological Societies, Barcelona, 2012 (Poster presentation).

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Egan K, Sena E, Vesterinen H, Macleod M (2011) Systematic review and meta-analysis of transgenic mouse models of Alzheimer's disease. Alzheimer's Drug Discovery Foundation Conference, San Diego, (Poster presentation, Young Investigator Scholarship awarded).

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Egan K, Sena E, Vesterinen H, Macleod M (2011) Probing the use of transgenic mouse models of AD: A systematic review and meta-analysis. Sackler PhD conference, Glasgow (Platform presentation).

List of Abbreviations

3xTgAD	Triple transgenic model
ACE	Adenbrooke's cognitive examination
AD	Alzheimer's Disease
ADAS-cog	The Alzheimer's Disease Assessment Scale Cognitive Behaviour Section
ADDF	Alzheimer's Disease Discovery Foundation
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
APPPS	Transgenic model with both APP and PS mutations
AVV	Adeno-viral vector
Aβ	Amyloid beta
BACE	Beta-secretase cleaving enzyme
CDR	Clinical dementia rating
Cl	Confidence limits
df	Degrees of freedom
DNA	Deoxyribonucleic acid
ELISA	Enzyme linked immunosorbant assay
EPM	Elevated plus maze
GFAP	Glial fibrillary acidic protein
GLP	Good laboratory practice
HPP	Hamster prion promoter
JCBFM	Journal of Cerebral Bloodflow and Metabolism
LPS	Lipopolysaccharide
LTP	Long term potentiation
MCI	Mild cognitive impairment

MMSE	Mini-mental state examination
MoCA	Motreal cognitive assessment
mPP	Murine prion promoter
MWM	Morris water maze
NFT	Neurofibrillary tangles
NMD	Normalised mean difference
NORT	Novel object recognition test
NSAID	Non-steroidal anti-inflammatory drug
PDGF	Platelet derived growth factor
Phos	Phosphorylation
PS1	Presenilin 1
RAWM	Radial arm water maze
SD	Standard deviation
SMD	Standardised mean difference

Abstract

The increasing prevalence of Alzheimer's disease poses a considerable socio-economic challenge in the years ahead. There are few clinical treatments available and none capable of halting or slowing the progressive nature of the condition. Despite decades of experimental research and testing over 300 interventions in transgenic mouse models of the condition, clinical success has remained elusive. Deepening our understanding of how such studies have been conducted is likely to provide insights which could inform future preclinical and clinical research. Therefore I performed a systematic review and meta-analysis on interventions tested in transgenic mouse models of Alzheimer's disease.

My systematic search was performed by electronically searching for publications reporting the efficacy of interventions tested in transgenic models of Alzheimer's disease. Across these publications I extracted data regarding study characteristics and reported study quality alongside outcome data for pathology (i.e. plaque burden, amyloid beta species, tau, cellular infiltrates and neurodegeneration) and neurobehaviour. From these data I calculated estimates of efficacy using random effects meta-analysis and subsequently investigated the potential impact of study quality and study characteristics on observed effect size.

My search identified 427 publications, 357 interventions and 55 transgenic models representing 11, 688 animals and 1774 experiments. There were a number of principal concerns regarding the dataset: (i) the reported study quality of such studies was relatively low; less than 1 in 5 publications reported blinded assessment of outcome or random allocation to group and no studies reported a sample size calculation, (ii) the depth of data on any individual intervention was relatively poor-only 16 interventions had outcomes described in 5 or more publications and (iii) publication bias analyses suggested 1 in 5 pathological and 1 in 7 neurobehavioural experiments remain unpublished.

Where I inspected relationships between outcomes, meta-regression identified a number of notable associations. Changes in amyloid beta 40 were reflective of changes in amyloid beta 42 ($R^2 = 0.84$, $p<0.01$) and within the Morris water maze changes in the 'training' acquisition phase could explain 44% of the changes in the probe 'test' phase ($p<0.05$). Additionally, I identified measures of neurodegeneration as the best pathological predictors of changes in neurobehaviour ($R^2 = 0.72$, $p<0.01$). Collectively this work identifies a number of potential weaknesses within *in vivo* modelling of Alzheimer's disease and demonstrates how the use of empirical data can inform both preclinical and clinical studies.

Chapter 1 Introduction

1.1 Brief Introduction

Alzheimer's disease (AD) has been a subject of curiosity for over two millennia. The ancient Greek philosophers Pythagoras, Hippocrates and Plato appreciated that mental deterioration is a feature of ageing and saw a mental state of infancy in old age was something 'common to all men' (Berchtold & Cotman 1998). Our first appreciation of dementia itself may have been as early as the 2nd century B.C. The Roman philosopher Cicero suggested that mental deterioration does not affect all old men equally, but those 'weak in will'. He eloquently demonstrated his appreciation of the delicacy of the aged mind, simultaneously suggesting preventative strategies for mental failure;

"it is our duty to resist old age; to compensate for its defects by a watchful care; to fight against it as we would fight against disease… . Much greater care is due to the mind and soul; for they, too, like lamps, grow dim with time, unless we keep them supplied with oil…. Intellectual activity gives buoyancy to the mind…. Old men retain their mental faculties, provided their interest and application continue…" (Berchtold & Cotman 1998).

Some two millennia later, in 1901 Bavarian psychiatrist Aloysius Alzheimer met Auguste Deter, a patient with an array of distressing symptoms. Once a relatively healthy individual, Auguste could not remember the simplest of memory tasks, had trouble sleeping and suffered from frequent delusional episodes (Maurer, Volk S., & Gerbaldo H. 1997). Alzheimer was curious, not only of her behaviour but also of the pathology. Similar cases followed, and at autopsy of such brains he noted a number

of common features: amyloid plaques, neurofibrillary tangles and neurodegeneration. One hundred years later our understanding of the differences between normal brain ageing and AD have advanced (Table 1.1) but there are a number of critical questions remain concerning; (i) causation, (ii) progression and (iii) potential methods of intervention (see later).

	Features of healthy brain ageing	Features of Alzheimer's disease
Behaviour	A degree of cognitive decline over the age of 65 is expected as a normal feature of ageing (Andrews-Hanna et al. 2007). However, effects are often subtle and do not generally impact on day to day living.	A gradual increase in the magnitude and frequency of memory loss. Typically presents with subtle semantic memory deficits and memory acquisition. Later stages of the condition are associated with poor general comprehension, severe memory impairments and loss of independent living (Förstl & Kurz 1999).
Neuropathology	While older non-demented individuals do not frequently present widespread plaques or tau tangles; evidence suggests some restricted AD pathology particularly in areas such as the neocortex, allocortex and basal ganglia (Morris et al. 1996;Thal, Del Tredici, & Braak 2004).	Staging of AD pathology defined by Braak stages. Amyloid plaque pathology originates from the neocortex and as disease progresses tau tangles and amyloid plaque pathology can be found across the brain including regions such as the hippocampus, cortex, midbrain and lower brain stem (Thal, Del Tredici, & Braak 2004).
	There is some evidence for both regional and widespread neuronal loss, however the impact is small in magnitude (Schuitemaker et al. 2012).	Ultimately AD causes extensive cell destruction and death (neurodegeneration). Neurodegeneration is overall non selective (Coleman & Flood 1987) but can impact greater on some brain regions greater than others (e.g. neocortex and hippocampal formation) (D'Amelio & Rossini 2012).

Table 1.1: A comparison of those features of Alzheimer's disease compared to normal cognitive decline in old age (See Sections 1.3 to 1.5 for further information).

1.2 The prevalence and impact of Alzheimer's disease

Today, Alzheimer's disease is estimated to affect more than 35 million individuals worldwide (Prince, 2009) and cases are typically observed in patients above 65 years of age. Estimates are that every 20 years these rates will double, meaning by the year 2050 Alzheimer's disease will affect 114 million individuals (Wimo et al. 2003). With one new case every seven seconds, we face an unprecedented social challenge; patients frequently need increasing assistance for daily activities which progresses to round the clock care in the later stages. The sacrifice caregivers make cannot be understated- managing the care of another who is consistently dependent can impact on entire families and the wider community. Equal to such social demands are the economics. The cost of dementia in a single year across Europe is currently thought to be more than €177 billion (Wimo et al. 2003). and the annual cost of a dementia patient is €20,000- exceeding the cost for both cancer and cardiovascular disease (Hampel et al. 2011).

1.3 Disease causation- genes or environment?

Much has been learnt from the 5% of the AD population where symptoms of the condition appear earlier in life (i.e. <65 years). While such patients are symptomatically indistinguishable from their older counterparts with AD, early onset is associated with a number of autosomal dominant mutations. Genetic linkage studies have identified three specific genes which are associated with the inheritance of early onset AD; amyloid β-protein precursor (APP) on chromosome

21, presenilin-1 (PS-1) on chromosome 14 (Sherrington et al. 1995) and presenilin-2 (PS-2) on chromosome 1 (Levy-Lahad et al. 1995) (Rogaev et al. 1995). The high prevalence of AD in Downs' syndrome (trisomy of chromosome 21) provides further evidence of the genetic component of the disorder.

For late onset Alzheimer's disease (>65 years), there is no definitive link between disease prevalence and environment or genetics (Alzheimer's Association Report 2012) however a number of risk factors have been identified; the greatest risk being advancing age. Others include: a family history of the condition, type II diabetes and lower attainment in education (Alzheimer's Association Report 2012). Genetic risk factors have also been identified, such as the apolipoprotein E (apoE) gene on chromosome 19. Those who inherit the E4 allele of apoE are at a greater risk of developing late onset of the condition compared to the general population, and have an earlier age of onset compared to those who inherit the E2 or E3 alleles (Corder et al. 1993;Saunders et al. 1993). Conversely the inheritance of the E2 allele has been suggested to be protective against the prevalence of AD(Corder et al. 1994).

1.4 The symptoms of Alzheimer's disease: a progressive neurodegenerative disorder

Alzheimer's disease is a slowly progressive neurodegenerative condition of the brain where the frequency and severity of behavioural and pathological abnormalities increase over time. Pathological changes are thought to precede behavioural changes, and thus numerous intervention strategies specifically target one or more of these features (see section 1.7 for more information on interventions).

Pathology

Prominent pathologies of AD include: an increase in amyloid levels which aggregate as amyloid plaques, tau neurofibrillary tangles, neuroinflammation and neurodegeneration. The slow progressive onset of such features is complex, multifactorial and our understanding is incomplete. The most widely accepted theory connecting the most prominent features of AD is the 'amyloid cascade hypothesis' (see Figure 1.1). This model is based on the rare autosomal inheritance of the condition but it is also thought to represent sporadic AD.

1.4.1 Amyloid cascade hypothesis and amyloid plaque pathology

Amyloid precursor protein (APP) is a single transmembrane peptide which undergoes post-translational modification by various secretase enzymes as part of normal metabolic processes throughout life (Seubert et al. 1992;Shoji et al. 1992). The

normal route of metabolism for APP involves non-amyloidogenic cleavage by α-secretase- producing an 83-residue C-terminal fragment (C83, [See Figure 1.1]) which upon further cleavage by γ-secretase leads to the accumulation of a small amyloid species known as p3 (Nunan & Small 2000). p3 is not thought to contribute to AD pathology and is relatively obscure.

An alternative sequence of events is thought to occur in AD. First, β-site APP cleaving enzyme (BACE) cleaves APP producing C99 and subsequent cleavage by γ-secretase (at the 42/43 site) produces amyloid species which aggregate in the extracellular space, forming 'amyloid plaques'. Amyloid species 40 and 42 amino acids long (amyloid beta 40 and amyloid beta 42 respectively) are thought to form the main constituent of such plaques, and amyloid beta 42 in the insoluble form is hypothesised to be particularly neurotoxic: with an ability to 'seed' the amyloid plaque (McGowan, Eriksen, & Hutton 2006). In recent years, there has been considerable interest in the impact of other amyloid assemblies such as monomers and oligomers; for example the 56-kDa soluble amyloid-β assembly has been shown correlate well with behavioural deficits in animal models of the condition (Lesne et al. 2006). Over time, plaque pathology is thought to become incrementally more robust. It remains unclear whether the causation of plaques is due to an increase in amyloid production or a reduction in clearance. Nevertheless, the widely accepted 'amyloid cascade hypothesis' (Hardy & Selkoe 2002) suggests that the resultant net imbalance triggers the consequential pathological and behavioural events in AD.

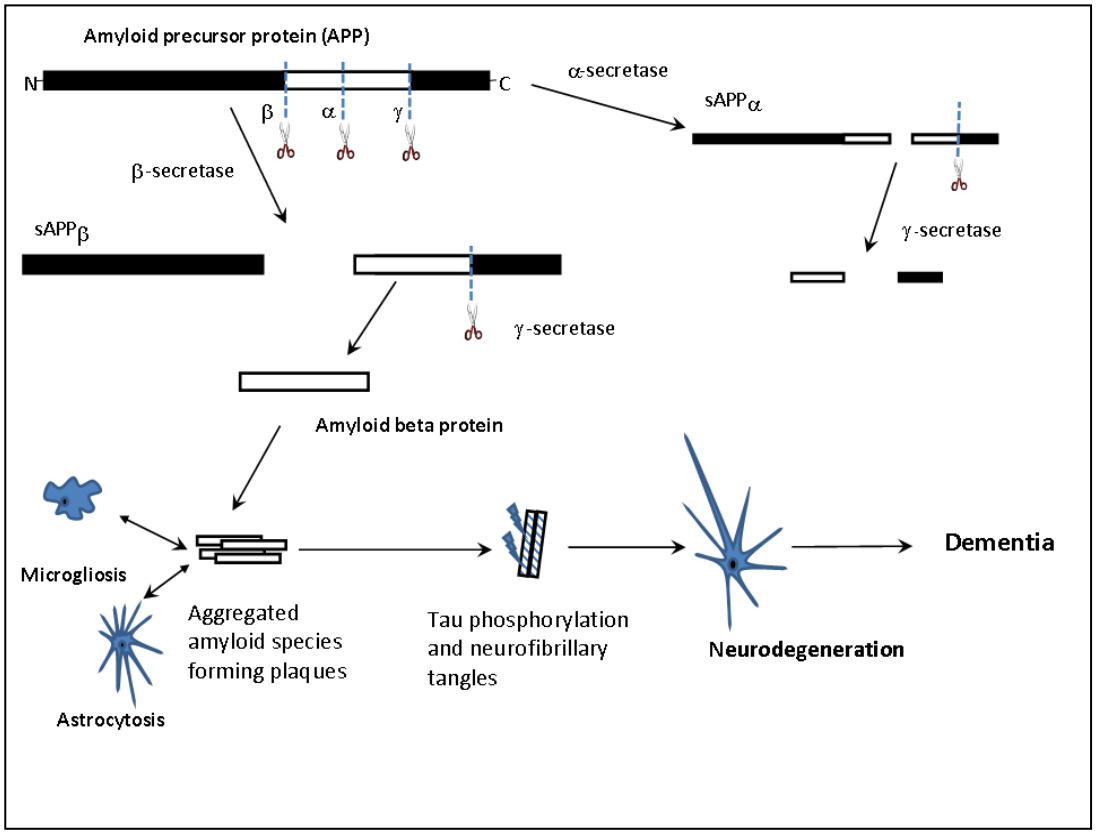


Figure 1.1: Amyloid precursor protein (APP) is normally cleaved by α and γ secretase leading to the formation of soluble APP (sAPPα). In Alzheimer's disease sequential cleavage by β and γ secretase leads to the aggregation of amyloid and the build of plaques. The 'amyloid cascade hypothesis' attributes the causation of Alzheimer's disease to an accumulation of amyloid beta aggregates, subsequently forming plaques and leading to the downstream phosphorylation of tau, progressive neurodegeneration and dementia. Diagram provides a simplified linear representation of sequential events; relationships may be more dynamic.

1.4.2 Tau neurofibrillary tangles

Tau is a multifunctional protein which is most commonly found localised to axons that stabilises microtubules. There are six isoforms of tau in the adult brain generated by alternative mRNA splicing and the protein has either three or four

sites (splicing dependent) capable of binding to microtubules (Johnson & Stoothoff 2004). Normal cell functionality permits various protein kinases (e.g. Cdk2, MAP kinase, GSK3) to phosphorylate tau protein (Baumann et al. 1993) which reduces the likelihood of tau binding to microtubules. In AD, this dynamic becomes destabilised and the hyperphosphorylation of tau (through one or numerous kinases) leads to an abundance of large non-membrane-bound abnormal fibres which occupy much of the perinuclear cytoplasm. Such fibres typically self-aggregate and form dense cores of insoluble tau in the form of 10-nm helices of 'paired helical filaments' (PHF) (Selkoe 2001). This aggregation severely impairs the ability of tau to bind to microtubules. Consequently, microtubules lose normal functionalities regarding structure and transport, and tau aggregates become sequestered elsewhere: by glial tangles, astrocytes and oligodendroglia. Hyperphosphorylation of tau is not unique to AD pathology. It is a common feature of Picks disease, frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration (Rademakers et al., 2004).

1.4.3 Neuroinflammation; microgliosis and astrocytosis

Chronic neuroinflammation is a hallmark feature of Alzheimer's disease; typically characterised by increased activity of both astrocytes and microglia Fuller (Fuller et al., 2010). Astrocytes are non-neuronal cells within the brain which support neurons with nutrients, monitor ion balance and induce neuronal repair after cell damage (Vincent et al. 2010). In AD, astrocyte activation has been attributed to neuronal

damage, neuroglial damage and the build up of extracellular amyloid (Verkhratsky et al. 2010;Wegiel et al. 2000). Astrocytes are frequently found activated in close proximity to plaques and are capable of inducing plaque clearance by recruiting amyloid degrading enzymes to plaque deposits (Verkhratsky, Olabarria, Noristani, Yeh, & Rodriguez 2010). Similar to astrocytosis, the presence of AD pathologies can cause microglial activation. In healthy brain tissue, microglia extensively survey neurons for damage, triggering repair, extracellular signalling or phagocytosis as required. AD pathologies activate microglia and thus become frequent components of amyloid plaques; where they are proposed to accumulate fragmented DNA.

Despite beneficiary roles, the precise role of astrocytosis and microgliosis in AD remains unclear. For example the positive effects of astrocyte activation may be short lived- it has been proposed that a build up of amyloid species can cause swelling and eventual lysis (Nagele, Andrea, Lee, Venkataraman, & Wang 2003).

Microgliosis has also been associated with detrimental effects such as the production of neurotoxic species which instigate neurodegeneration (McGeer & McGeer 1995;Streit 2010). It also could be that astrocytes and microglia, when activated represent opposing forces. Evidence from post mortem AD brains has suggested that microglia may be responsible for plaque formation but astrocytosis is responsible for plaque degradation (Wegiel, Wang, Tarnawski, & Lach 2000).

Notwithstanding such uncertainties, it must be emphasised that the inflammatory response in AD pathology is both chronic and widespread and the impact (positive or negative) could influence behavioural outcomes. It is thought that such an extent of neuroinflammation is capable of impairing the integration neuronal signals (Nagele et al. 2003;Vincent, Gasperini, Foa, & Small 2010) and recent evidence suggests that the extent of microgliosis in the brain correlates well with cognitive performance in AD patients (Mrak 2012).

1.4.4 Neurodegeneration

Collectively, the disturbances across AD pathology are thought to cause neurodegeneration; the incremental inhibition of normal cell function, connectivity and consequential programmed cell death. The manifestation of AD symptoms are thought to initially decrease neuronal cell functionality and plasticity; such as the capacity for long term potentiation (LTP) within hippocampal cells (Chen et al. 2000) or the prevalence of those proteins required for synaptic integrity (such as synaptophysin); both of which are likely contributors to the subsequent neuronal loss. While the brain may be 100 billion neurons strong before the presence of AD pathologies take hold (D'Amelio & Rossini 2012) sustained ubiquitous neuronal loss (opposed to selective loss observed in neurodegenerative Parkinson's disease) over time, can severely disrupt neuronal networks- and have impact in regions critical for semantic memory such as the cerebral cortex and hippocampus. Precisely how this occurs is unclear; one proposed mechanism is that damage sensors present on cell organelles such as the nucleus and golgi apparatus become activated and trigger

neuronal cell death signals, 'caspases' through both extrinsic and intrinsic pathways (Bredesen 2009). A summary of neurodegeneration features is shown in Figure 1.2.

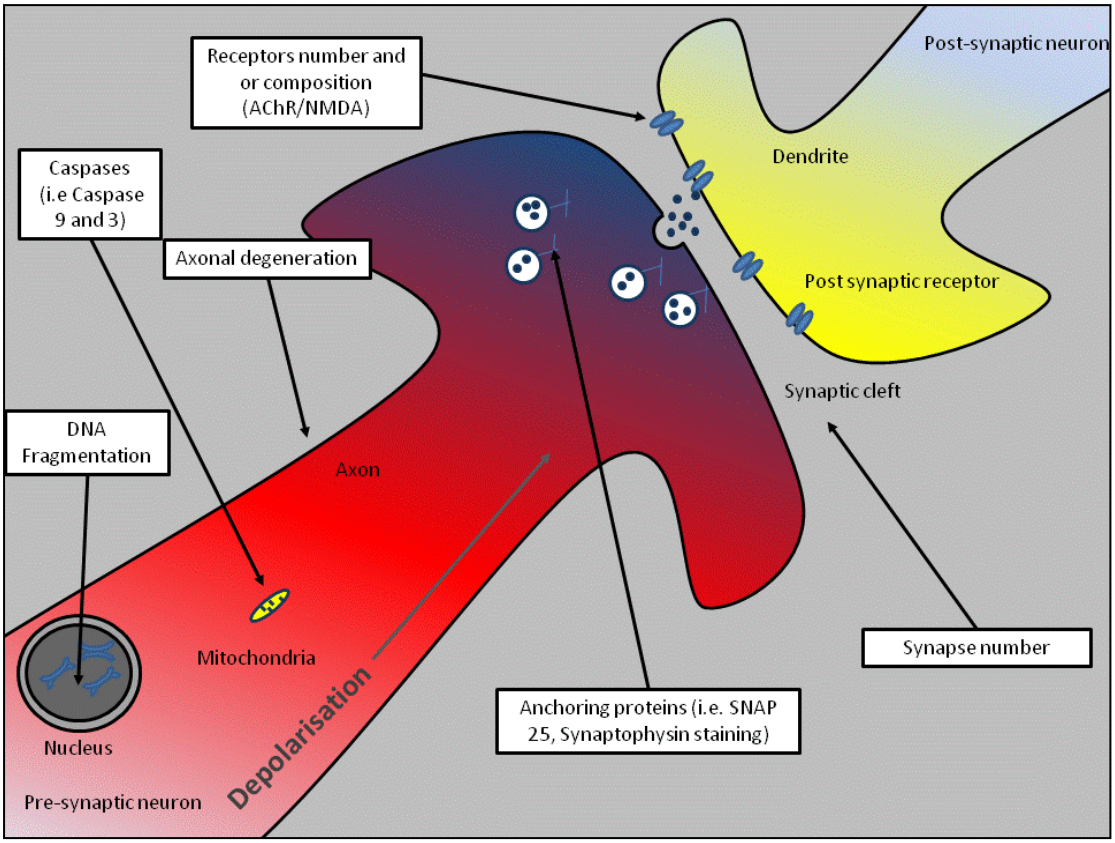


Figure 1.2: A representative selection of the outcome measures related to end points include features such as: DNA damage, caspase activity, the loss of synapses and neurons, axonal degeneration, DNA fragmentation, cell death signalling (through Caspase-3 and Caspase-9), synaptic anchoring proteins (snaptoyphysin, SNAP 25) and post synaptic receptor number or subunit composition. NMDA; N-methyl-D-aspartate, AchR; Acetylcholine.

1.5 Behavioural symptoms

The progression of Alzheimer's disease can take years if not decades to manifest and is characterised clinically by specific stages (See Figure 1.3). Early diagnosis of the condition remains difficult and progression from one phase to the next may not occur within the patients' lifetime.

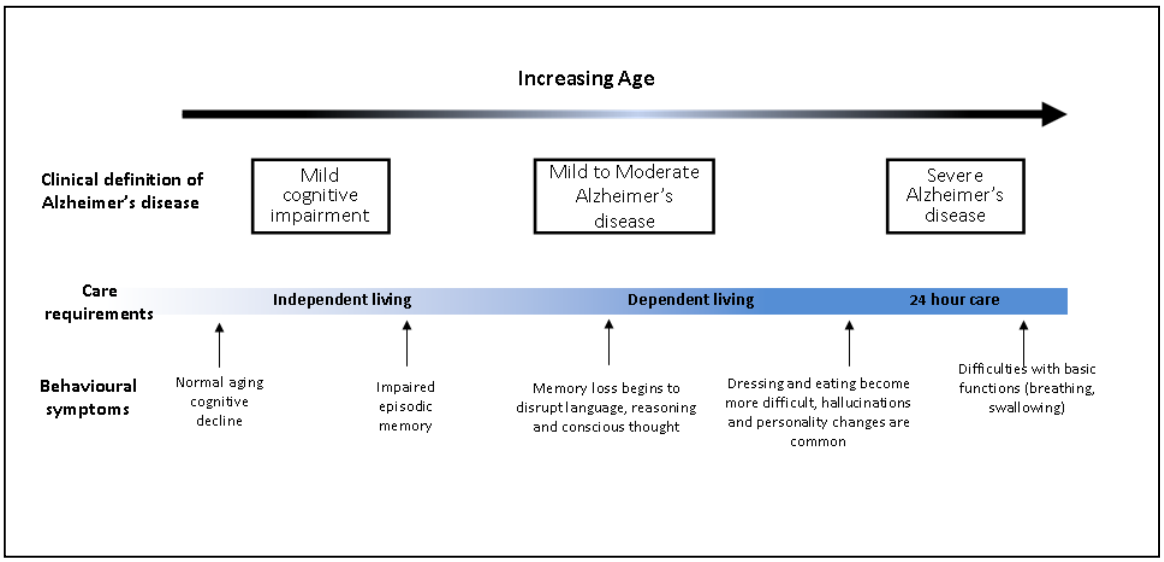


Figure 1.3: The progression of Alzheimer disease (AD) in clinical terms reflects the progressive loss of normal behavioural functions. While a degree of cognitive decline is expected in the older ages of life in AD patients may ultimately have impaired speech and loose the capacity to perform normal daily activities such as washing and dressing.

The earliest stages of AD are associated with difficulties in acquiring new information and the use of semantic memory (Förstl & Kurz 1999). Diagnosis is often difficult; symptoms can be subtle and may be overcome through memory aids or coping strategies- even well established behavioural assessment techniques such as the activities of daily living (ADL) can be incapable of detecting such changes.

In the clinic, the earliest phase at which behavioural symptoms can be identified is mild cognitive impairment (MCI). Briefly, a diagnosis of MCI is based on; (1) changes in cognition observed by either the individual or an observer; (2) object impairment in one or more cognitive domains; (3) independent in functional activities and the diagnosis must be made the absence of dementia (Morris 2012). As the condition develops (notably, MCI may never progress to AD within a patients' lifetime) subtle memory issues become more prominent (e.g. increased frequency of recognition or finance errors) and progress towards symptoms of Alzheimer's disease.

1.5.2 Mild Alzheimer's disease

The diagnostic criteria for suspected Alzheimer's disease are variable and there are numerous scales currently in use: the most common criteria stipulate deficits both in memory and in at least one other cognitive domain (Alves et al. 2012). Methods for assessing AD behaviour through cognitive function include the Mini-mental state examination (MMSE) (Folstein, Folstein, & McHugh 1975), The Alzheimer's Disease Assessment Scale Cognitive Behaviour Section (ADAS-cog) (Cano et al. 2010), the Clinical dementia rating (CDR), Adenbrooke's cognitive examination (ACE)(Kipps and Hodges, 2005) and the Montreal cognitive assessment (MoCA) (Freitas et al., 2012). In practical terms, diagnosis is not always straight forward; successful diagnosis rates of AD vary from 50% outside specialised centres to 95% with experienced clinicians (Mayeux et al. 2011) and the true diagnosis of AD can only be made at post-mortem.

1.5.3 Severe Alzheimer's disease

The behavioural capabilities of the AD patient diminish progressively as the disease advances. Later stages of the disease are associated with difficulties in performing daily activities and general comprehension. Frequent symptoms include; aimless or restless activity, sleeplessness and aggressive episodes. One fifth of patients are also thought to suffer from hallucinations. While AD is unlikely to directly cause death, the presence of the condition will reduce life expectancy by one third (Förstl & Kurz 1999) . Death most often occurs due to complications such as myocardial infarction and septicaemia.

1.6 Linking the progression of pathology to behaviour

One aim of AD research is to link the molecular progression with the behavioural phenotype. Despite comprehensive studies regarding the progressive staging of AD pathology at autopsy (Braak & Braak 1991) and the widely accepted 'amyloid cascade hypothesis' there is no universal agreement as to which species is responsible for instigating the process. Further, despite a number of studies correlating specific pathologies with cognitive decline I are yet to conclusively define which pathological feature(s) of AD correlate with cognitive decline (Parvathy et al. 2001;Matthews 2006;McGowan, Eriksen, & Hutton 2006;Nelson, Braak, & Markesbery 2009).

In spite of this limitation, it is understood that pathological changes precede the clinical diagnosis of dementia by years if not decades (Morris 2005). As we cannot predict who will develop AD, current clinical trials are based on reducing well established AD pathologies. Such a limitation may have important implications, as neurodegeneration is often well established in the later stages of condition. This issue has encouraged extensive efforts into developing successful biomarkers for AD such as Pittsburgh compound B (Klunk et al. 2004) in order to allow early identification of AD.

1.7 The search for novel clinical candidates

1.7.1 Clinical treatments

Despite our best effects as a research community, there are no clinical treatments capable of halting (or even slowing) the progression of AD. A small number of treatments are available which can provide limited cognitive benefits such as Donepezil and tetrahydroaminoacridine. These interventions work by increasing acetylcholine levels in the synaptic cleft thus increase the likelihood of action potential propagation. In more severe stages the NMDA antagonist Memantine may be prescribed which acts as a nicotinic acetylcholine receptor antagonist, ultimately causing an up-regulation of the receptor. Collectively, these interventions do not address the causation of the disorder; benefits are frequently short lived, and some patients may see no benefit at all (Selkoe 2001). Thus the search for novel cognitive stimulants and treatments capable of slowing or stopping the underlying pathology is an urgent unmet medical need.

Clinical trial design over the last two decades has generally been based around targets identified from the amyloid cascade hypothesis. For example, promoting amyloid beta clearance has been an area of focus through both active and passive immunisation strategies which solubilise amyloid, promote phagocytosis or use antibodies to remove amyloid deposits from the brain (Mangialasche et al. 2010). Particular promise for active immunisation emerged from a phase 2 randomised

control clinical trial of AN-1972(QS-21), where immunisation with the A-beta-42 peptide induced significant levels of anti-amyloid titres. While the trial had to be halted early due to aseptic meningoencephalitis which developed in around 6% of patients, numerous follow up studies found reduced AD pathology in treated patients, and many speculate that the adverse reaction was due to the adjuvant -not the peptide (Tabira 2010).

Preventing amyloid production and its aggregation is another strategy which underpins clinical trial design. Non-steroidal anti inflammatory drugs (NSAIDS) used to target the γ-secretase cleavage site of APP and β-secretase inhibitors such as Rosiglitazone or Pioglitazone have been used to attempt to lower the initial production of amyloid beta. Targeting tau protein has been another key area of research and both *in vitro* and *in vivo* investigations using Minocycline have identified that the intervention can modulate tau phosphorylation, aggregation and decrease neuronal death and cognitive decline (Noble et al. 2009).

1.8 Animal models of Alzheimer's disease

Across Alzheimer's disease the identification of clinical candidates (and aspects of clinical trial design) owe much to the animal modelling of the condition. Numerous animal models have been developed; capturing aspects of the human condition, each with specific attributes. *Drosophila melanogaster (D. melanogaster)* models have emerged as particularly useful tools for studying AD neurodegeneration. With a highly conserved genetic sequence to humans, gene knock down or transgene

experiments have provided insights into the development of both plaque and tau pathology (Van Dam & De Deyn 2011). Similarly, *Canorhabditis elegans (C.elegans)* have a number of genetic homologues with humans (notably PSEN1), and both aspects of plaque and tau pathology can be recaptured in transgenic models. Despite their successes both of these organisms have substantial differences in brain anatomy from humans and behavioural assessments are often limited (Gotz et al. 2004). Rodent models with pathological and behavioural features of AD have also been developed through the injection of amyloid fragments to induce the AD phenotype (Frautschy et al. 1996;Nitta et al. 1994) but faithful replication of such models has proved difficult. The most frequently used animal model of AD for testing interventions is undoubtedly, the transgenic mouse model (see next).

1.8.1 Transgenic mouse models of Alzheimer's disease

Following the identification of familial AD and those mutated genes responsible, transgenic mouse models were engineered with the aim to recapture aspects of AD *in vivo*. The first transgenic mouse model was engineered in 1995 (Games et al. 1995) where the over expression of a mutated APP (V717F mutation driven by the platelet derived growth factor promoter) produced a phenotype of amyloid plaques and neuronal loss. Subsequently, there has been an array of models produced, including models based on the expression of transgenic presenilin (PS) (Janus et al. 2000); or both APP and PS each with specific AD like pathologies alongside behavioural deficits (Bridget et al. 2002). Collectively, such work culminated in crossing APP, PS and Tau lines to produce a triple transgenic model (3xTgAD), capable of capturing;

tau neurofibrillary tangles, aggressive amyloid plaques and cognitive deficits (Oddo et al. 2003). The molecular success of transgenic mouse models has been well reflected by extensive use to test candidate intervention strategies before reaching the clinical trial stage (Zahs & Ashe 2010). Both behavioural end points (e.g. paradigms such as the Morris water maze (Morris 1984)) and pathological end points (e.g. Enzyme-linked immunosorbent assay (ELISA) for amyloid levels, immunohistochemistry for plaques) can be quantified and efficacy determined by comparing control and treatment groups.

1.9 Translational failure in Alzheimer's disease

The prospect of testing candidate intervention strategies in animal models capable of capturing aspects of AD provides two main advantages, an opportunity to: (i) demonstrate efficacy *in vivo* and (ii) investigate molecular mechanisms. While transgenic mouse models have considerably advanced our understanding of AD, issues have arisen regarding reproducibility of efficacy in the clinical trial stage. This issue was well illustrated by Ashe and colleagues (Zahs & Ashe 2010) who demonstrated that over 300 interventions had been tested in the Tg2576 mouse alone without clinical success. Indeed, no novel clinical treatments have emerged in AD despite over a decade of testing therapeutics in these transgenic animals.

1.10 Issues in the use of transgenic mouse models of Alzheimer's disease

The translational road block observed in AD has caused many concerns regarding both the external validity and the internal validity of preclinical and clinical studies.

For example, there are numerous concerns regarding the way in which transgenic mice are produced; over-expression of APP is not a clinical feature of the condition and the rapid onset of pathology in transgenic mice may take more than 60 years to manifest in humans. Despite the advances in our ability to produce an array of different models, none of these have been identified as the 'gold standard'; each transgenic model captures a specific array and severity of symptoms.

While model criticisms may question the overall use of transgenic mice in order to predict clinical efficacy, there are a number of noteworthy alternative explanations regarding translational failure. For example, as interventions are frequently given early in the mouse lifespan, this may mean that we are learning how to prevent AD opposed to treating it (Zahs & Ashe 2010). Further, methodological variation within pre-clinical AD studies is anticipated to be high (Vorhees & Williams 2006); if studies do not reflect the design of the clinical trial we may be reducing the likelihood of clinical success.

In pre-clinical studies of AD there have been no systematic studies of methodology or quality concerning transgenic mouse models of the condition. Further, it is not known whether there is evidence of publication bias in the pre-clinical literature (the lack of published papers with negative or neutral findings) which could inadvertently misinform clinical trials in AD through overstating efficacies.

Collectively, we have to accept the possibility that biological truths are not being reflected in experimental results at either the preclinical (Figure 1.4) or clinical trial stage (Figure 1.5) . Altenatively it could be that translational failure occurs because the biological truths from animal experiments do not equal those found in humans (Table 1.6). A deeper understanding of transgenic model studies may provide evidence to help address such questions while simultaneously aiding the design of future pre-clinical and clinical trials in AD.

	Efficacy reported in preclinical trial	Efficacy not reported in preclinical trial
Truly positive studies	Positive preclinical trial results are a faithful representation of the biological truth.	Preclinical trials are falsely negative. Possible reasons for this may include inappropriate outcome measure selection, random chance, selection bias or compliance issues.
Truly negative studies	Preclinical studies are falsely positive where no true efficacy exists. Plausible reasons for this include: random chance, publication bias or a study quality bias	Negative preclinical trial results are a faithful representation of the biological truth.

Figure 1.4: The reported results from preclinical trials many be biologically untrue. This could be one explanation of the translational failure observed for internvetions in Alzheimer's disease. Each of the possible scenarios of biological vs. experimental truth is explained further.

	Efficacy reported in clinical trial	Efficacy not reported in clinical trial
Truly positive studies	Positive clinical trial results are a faithful representation of the biological truth.	Clinical trials are falsely negative. Possible reasons for this may include issues regarding the selection of the trial population, outcome measure based issues, compliance or other biases such as study quality.
Truly negative studies	Clinical trials are falsely positive. Possible reasons may include: insufficient sample size, random chance, outcome measure selection, publication bias and study quality bias	Negative clinical trial results are a faithful representation of the biological truth.

Figure 1.5: The reported results from clinical trials could be biologically untrue. This could be one explanation of the translational failure observed for internvetions in Alzheimer's disease. Each of the possible scenarios of biological vs. experimental truth is explained further.

	Efficacy reported in preclinical trials	Efficacy not reported in preclinical trials
Efficacy reported in clinical trials	Positive preclinical trial results are a faithful representation of the biological truth in clinical trials. Transgenic mice are good predictors of clinical efficacy.	Preclinical studies are falsely negative. Plausible reasons for this may include: construct validity issues, inappropriate outcome measure selection, random chance or study quality bias.
Efficacy not reported in clinical trials	Preclinical studies demonstrate efficacy which is not reported in clinical trials. Plausible reasons for this could include: random chance, publication bias, study quality bias or construct validity issues.	Negative preclinical trial results are a faithful representation of the biological truth in clinical trials. Transgenic mice are good predictors of clinical efficacy.

Figure 1.6: The reported results from preclinical trials may not reflect those results fom the clinical trial stage. This could be one explanation of the translational failure observed for internvetions in Alzheimer's disease. Each of the possible scenarios of preclinical vs. clinical reporting is explained further.

1.11 Systematic review and meta-analysis

The issue of translational failure is not unique to AD; such a challenge has been identified in other neurological disorders (e.g. ischemic stroke, Parkinson's disease, multiple sclerosis) and beyond (e.g. myocardial infarction). For a number of these conditions, systematic review and meta-analysis techniques have proved useful tools in order to improve our understanding of translational failure (Rooke et al. 2011;Sena et al. 2007a;Vesterinen et al. 2010).

A systematic review provides a transparent method by which to identify how much literature exists within a given field of research. Studies generally state: the pre-specified inclusion criteria, specific search terms used, databases searched and how the number of included studies was achieved which makes the method reproducible. Where multiple experiments have been conducted meta-analysis can provide a method of pooling data together in order to summarise how well interventions perform. Using these pooled estimates of effect; meta-analysis can also inspect relationships between variables (e.g. does the age at administration affect observed outcomes?).

Thus, performing a systematic review and meta-analysis of those interventions tested in transgenic mouse models of AD is likely to provide a number of benefits, such as a comprehensive summary of: interventions tested, transgenic mouse models used and reported study quality. Alongside identifying conducted studies,

techniques used may help identify gaps in knowledge (e.g. a promising intervention has not been tested for efficacy against a key feature of AD); or suggest new hypotheses for exploration (e.g. two separate interventions are likely to provide effective combination therapy). Additionally, data collected could be used to help provide a framework on which to separate 'moderate' from 'excellent' behavioural performance for different experimental groups (e.g. control transgenic or wild type) when testing emerging clinical candidates.

In animal models of focal ischemia systematic review work has previously identified that the reported study quality in pre-clinical studies is relatively low (such as presence of blinding, randomisation) (Macleod 2008) .Subsequent meta-analysis suggested that experiments with low study quality were associated with higher estimates of efficacy and it is likely I can address similar questions within preclinical AD

Meta-analysis can also provide useful insights into whether aspects of study methodologies can impact on observed outcome. For example, a frequent finding in animal models of stroke is that delays in time to treatment are associated with lower estimates of efficacy (Sena et al. 2007b). For models in AD, analyses could inspect model specific features such as whether age and/or specific transgenes are associated with greater or lesser estimates of efficacy. Further, meta-regression can provide evidence-based hypotheses regarding relationships both within (e.g. does

behavioural training ability determine behavioural test performance?) and between outcome measures (i.e. can changes in plaque burden explain changes in tau?). Meta-analysis can also be used in order to investigate whether publication bias exists in preclinical literature and the potential magnitude of impact. For example, 'trim and fill' techniques have been used previously to impute the extent of missing papers and the magnitude of revised efficacy (Sena et al., 2010b). Collectively, systematic review and meta-analysis work in stroke has culminated in the production of 'Good laboratory practice (GLP) guidelines' which provide guidelines for robust pre-clinical trial design (Macleod et al. 2009). While there have been some guidelines recently published for performing pre-clinical studies in AD (Shineman et al. 2011) these have been based primarily on an expert panel opinion. Therefore, this work will provide the first evidence based approach in order to improve the design of trials AD.

1.12 Aims and objectives

The applicability and utility of systematic review and meta-analysis have been well demonstrated in recent years. Building on such use, this thesis is written with the primary aim of using existing data to provide evidence to develop evidence based GLP guidelines in order to make best use of transgenic mouse models of Alzheimer's disease.

This thesis is laid out with particular focus on the cardinal behavioural and pathological features of Alzheimer's disease. The methodologies of the systematic

review and meta-analyses performed are first explained (Chapter 2) and Chapter 3 summarises the results of our systematic search by outcomes, interventions and transgenic models. For meta-analyses results, chapters are organised into specific objectives including analyses on: individual outcome measures (Chapter 4); transgenic mouse models (Chapter 5) and interventions (Chapter 6). Chapter 7 addresses our objective to understand the impact of study quality and publication bias on observed results. During the course of study I have worked on a number of other significant (and published) projects within translational failure and Chapter 8 summarises some prominent pieces of work. Finally, Chapter 9 brings together findings across all chapters and provides a further narrative critique.

Additionally there a number of appendices attached to this thesis. Appendix I provides the comprehensive list of those studies included in the systematic review, Appendix II describes the reported study quality of such articles whereas Appendix III describes the methodology of experiments included in meta-analyses. Further, I include notes from my experimental work in the Morris laboratory in Appendix IV.

Chapter 2 Methods

In this chapter I discuss how the systematic search was performed and subsequent data extraction. The methodologies of meta-analysis are explained including effect size calculations, weighting and how data were used to provide summary estimates and assess sources of heterogeneity. The various methodological techniques used to assess publication bias are also discussed.

2.1 Systematic search

Studies testing interventions in transgenic mouse models in AD were identified from Pubmed, EMBASE and ISI Web of knowledge with the search terms ['targeted deletion' OR 'overexpression' OR 'knock out' OR 'vector' OR 'transgenic'] AND ['dementia' OR 'tau' OR 'mild cognitive impairment' OR 'Alzheimer's disease'] within the limit 'animals'. The search was conducted in January 2009 and publications limited to 1995 onwards (the year the first transgenic AD mouse model was published).

2.2 Inclusion and exclusion criteria

Titles and abstracts of identified publications were screened by two independent reviewers (KE and MM). We retained studies that reported the testing of any intervention in any amyloid, tau or presenilin based transgenic mouse model of AD. Mice with additional genetic manipulations (e.g. COX-2 knockout) were not included in the systematic search as I envisaged that they have limited relevance to

the clinical setting. MM and I excluded publications without an appropriate control, and did not include combination therapies. Ovariectomised transgenic mice were considered a mechanism of model development and thus MM and I included such studies in the review. For studies reporting active immunisation with amyloid beta peptides, I categorised interventions based on the fragments of Aβ used and also extracted additional details regarding of vectors and/or modifications.

2.3 Data extraction

From the publications included in our review I extracted details regarding: author, year of publication and journal. I assessed study quality using a five item checklist where studies were given one point for each criterion met. As this is the first study of its kind of the AD field, selected checklist items were those which had demonstrated significant impact on observed outcomes in preclinical studies elsewhere (blinding and randomisation- Macleod, 2008) and those crucial for statistical power (sample size calculations). Alongside these I chose to include (i) compliance with animal welfare legislation (to identify whether the overall treatment of the animals might impact on observed effects) and (ii) a statement regarding conflicts of interest (to identify whether alternative motives might be associated with differences in estimates of efficacy).

I also extracted details on the model used, intervention and outcome assessed. Model details included: background strain of mouse, transgenic model, promoter and sex. Intervention details included: intervention name, dose, route of administration, frequency of administration (i.e. single, multiple, continuous), and the age of the animal at intervention administration and outcome assessment (days).

For outcomes of interest I extracted the number of animals used, mean and corresponding variance for control, treatment and wild type values wherever present. I preferentially used data values given in text or tables and where these were not available, I extracted data from graphs using Universal Desktop Ruler 3.2; calibrated for each individual graph. Where a single control group serves multiple treatment groups, the size of the control group was adjusted by division by the number of treatment groups served for meta-analysis.

A common occurrence in experimental science is that multiple controls are used and I needed to ensure continuity across data extraction. Therefore I used a priority rule wherever more than one 'control' exists. I preferentially extracted control data in the order; (i) where part of the delivery mechanism is included (e.g. example an adjuvant or empty vector), (ii) saline or non-treated controls. If no suitable control existed within a given publication then it was excluded from the systematic review.

2.3.1 Pathological outcomes

Pathological outcomes of interest were: (1) plaque burden, (2) amyloid beta species, (3) tau NFT, (4) neurodegeneration, and (5) cellular infiltrates;

(1) I included all plaque staining related outcomes regardless of staining technique or methodology of counting used (number, density and area). As plaque pathology is typically extracellular, I did not include intracellular plaques in our analyses (Gimenez-Llort et al., 2007)

(2) I extracted details regarding all amyloid species including: amyloid beta 40, amyloid beta 42, total amyloid and oligomers. I extracted data regardless of solubility or method of quantification. Where data were recorded as short term transient changes (i.e. across 24 hours) I took the largest reduction of amyloid observed in order to prevent unduly punishing proof of concept studies where amyloid levels are allowed to return to normal. Due to the transient nature of CSF amyloid levels I did not extract such data (Bateman et al., 2007).

(3) For tau NFT, I extracted both overall changes in tau and phosphorylation states. I included all data regardless of method of quantification (e.g. ELISA, immunohistochemistry, western blot).

(4) Irrespective of staining technique or method of quantification I extracted data regarding both astrocytosis and microgliosis, hereafter referred to as, "Cellular infiltrates". Where data regarding cellular infiltrates were presented with other features such as plaques, I preferentially extracted cellular infiltrate outcome measures in isolation opposed to co-staining techniques.

(5) I extracted all outcome measures of neuronal degeneration, including direct markers (e.g. the loss of neurons) and indirect markers (e.g. capspase-3, See Chapter 3 for a summary). I also included neuronal regeneration (i.e. neurogenesis) under the comprehension that the outcome measure provides an alternative perspective regarding neuronal plasticity (Chuang, 2010, Lazarov and Marr, 2010).

2.3.2 Neurobehavioral outcomes

I extracted data from all behavioural paradigms identified within the literature and for each I extracted data regarding the last identifiable time point for each paradigm (clinically, longer term outcomes are likely to be of greater interest). Where a single paradigm had multiple components which address different questions (e.g. cued and contextual learning with fear conditioning paradigm) I extracted the last time

point given for each individual question addressed. I did not extract reversal task behaviour as I perceived this to be a secondary objective of behavioural paradigms.

Where experiments were performed in the (1) Morris water maze (MWM), (2) novel object recognition test and (3) radial arm water maze (RAWM) there were additional data extraction rules made;

(1) For MWM outcomes I captured data from both the acquisition and probe phase. For the acquisition phase I extracted all time points providing the position of the platform remains constant throughout the test for path length and latency outcomes. For the probe test where MWM outcomes were reported serially I only include data for the last time point (unless experiments only provide a summary estimate of probe performance where this would be taken forward). I did not include data for reversal task behaviour or for time in opposite or adjacent quadrants.

(2) I included a number of alternations to the novel object recognition test including object replacement test and object shape test (variations summarised in Chapter 3). Methods of assessment in the novel object recognition task include a number of outcomes which share interdependency with each another (e.g. time with new object and time with old object). To avoid over representing of experimental data (which would cause increased weight) I preferentially extracted one outcome in the order;

(i) discrimination index, (ii) time with novel object and (iii) time with familiar object.

(3) Similar to the novel object recognition test, the RAWM can be assessed using parameters which have a degree of interdependence (e.g. reference memory, working memory). Therefore I preferentially extracted total error opposed to reference and working memory components.

2.4 Meta-analysis

Meta-analysis provides a statistical method whereby results from multiple trials can be combined to provide summary estimates of effect. Such estimates can be used in order to analyse the potential impact methodology has on observed outcomes. There are a number of stages in performing meta-analyses presented (see Figure 2.1 for overview). First, individual estimates of effect size must be obtained. Studies are then combined and weighted (to ensure smaller imprecise studies do not contribute equally to the overall estimate as larger precise studies).

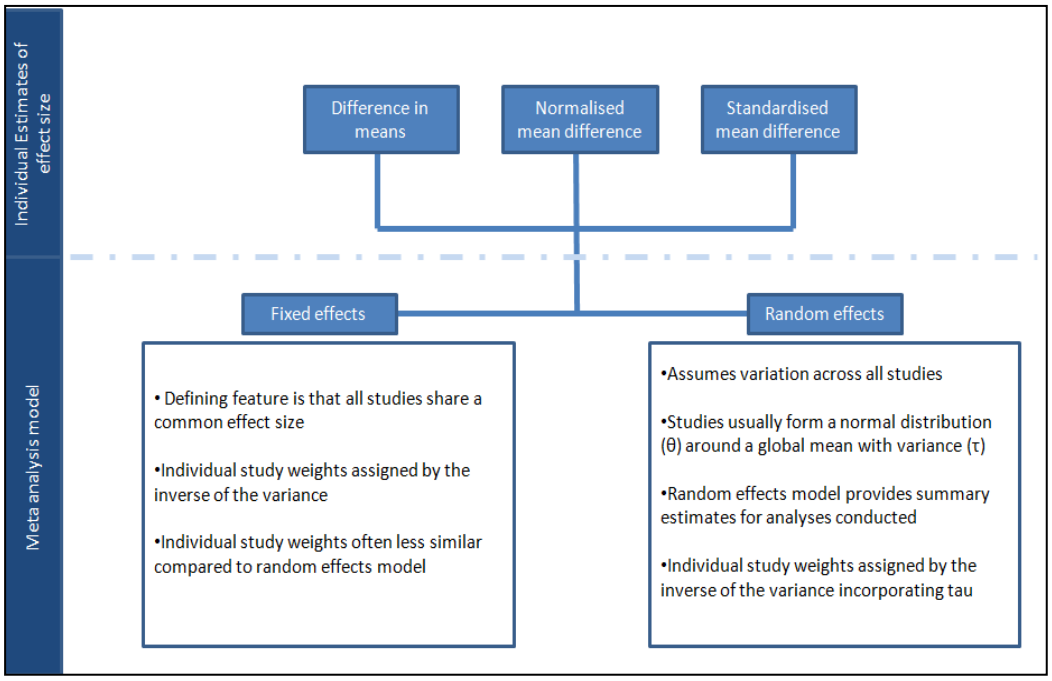


Figure 2.1: There are a number of stages performed in meta-analyses calculation. Estimates of efficacy are first calculated at the individual study level. Data are subsequently either entered into the fixed or random effects model. The random and fixed effects models make different assumptions on data (see section 2.4.3, adapted from (Borenstein et al., 2009))

2.4.1 Definition of a comparison

I defined a comparison as an outcome measured in a group of treated transgenic animals compared with outcome in a group of untreated control transgenic animals. Where there is more than one estimate present for the same structural or behavioural outcome of interest within the same cohort of animals, I first combine data using fixed effects meta-analysis to give an overall estimate of efficacy.

For calculating effect sizes within the acquisition phase of the MWM I made an exception to the last time point rule (extracting behavioural data at the last time point) for behavioural paradigms. This was because selecting a single time point within the acquisition phase may not provide a faithful representation of overall training performance. Therefore, I combined multiple measurements within the acquisition phase of the MWM to estimate efficacy. For these, I limited calculations made to 'latency' or 'path length' (as these were the most frequently reported- See chapter 3.10) and calculated the area under the curve using the trapezoidal rule for both control and treatment groups. Thus the area under each curve (AUC) was calculated by;

$$AUC = (n[C_{Mean}] - 0.5([C_{FTP}] + [C_{LTP}]) \qquad (2.1)$$

Where; C_{Mean}= The mean value of all the curve data points
C_{FTP} = The first data point of curve
C_{LTP} = The last data point of curve

Where I calculate the variance accounting for both within and between study variance with the equation;

$$\sigma = \sqrt{\sum(\chi - \bar{\chi})^2 + \sum(\theta_i)^2} \quad (2.2)$$

Where; $\bar{\chi}$ = The mean value of all the curve data points
χ = Individual point estimates of data points
θ_i = Standard deviation of each data point within curve

2.4.2 Individual effect size estimates

There are three principle methods for calculating effect size; a simple difference in means meta-analysis (MD), a normalised difference in means (NMD) and a standardised difference in means (SMD). The choice of method is dependent on the dataset in question. For example, difference in means estimates can be used where outcomes are measured on the same scale. While this technique is advantageous because effect sizes directly relate to experimental results, the likelihood of all experiments using the same scale in preclinical science is relatively limited. An alternative method is NMD where experiments using different scales can be combined by estimating the effect relative to the difference between a disease model and wild type animal. Again, this technique is fairly straight forward to comprehend but wild type behaviour must be stated (or imputed) for the technique to work. Finally, SMD estimates of effect can also combine data using different scales by basing the effect size on the variance of a given study. The technique does

not require knowledge of wild type performance and assumes differences in variance between trials are a reflection of differences in measurement scales- not the study population (Borenstein et al., 2009).

(i) Difference in means meta-analysis (MD)

Difference in means effect size (see Equations 2.3 and 2.4) is calculated by the difference between an intervention mean (m_{Rx}) minus the control mean (m_c). Such methodology is particularly suited to data where all data are on the same scale and where different experiments have identical sensitiveness.

$$MD_i = m_c - m_{Rx} \tag{2.3}$$

Where m_c = mean in control group
m_{Rx} = mean in treatment group

With standard error;

$$SE(MD_i) = \sqrt{\frac{SD_c^2}{n_c} + \frac{SD_{Rx}^2}{n_{Rx}}} \tag{2.4}$$

Where SD_c = Standard deviation in treatment
SD_{Rx} = Standard deviation in control
n_c = number of control animals
n_c = number of treatment animals

(ii) Normalised mean difference (NMD) meta-analysis

Normalised mean difference meta-analysis express individual effect sizes as a percentage improvement (Equations 2.5 and 2.6). The estimation of effect size is underpinned by the difference between the lesion model and wild type behaviour. An improvement which reached that of wild type performance would have an effect size of 100.

$$NMD = \frac{(m_c - m_{wt}) - (m_{Rx} - m_{wt})}{(m_c - m_{wt})} * 100 \qquad (2.5)$$

Where; m_c = Mean in control group
m_{Rx} = Mean in treatment group
m_{wt} = Mean in wild type group

With standard error;

$$SE(NMD_i) = \sqrt{\frac{SD_{Rx}^2}{n_{Rx}} + \frac{SD_c^2}{n_c}} \qquad (2.6)$$

Where SD_{Rx} = Standard deviation in treatment
SD_C = Standard deviation in control

(iii) Standardised mean difference meta-analysis

Standardised mean difference (SMD) meta-analysis calculation of effect size can be particularly useful where numerous different scales are used to assess the same outcome (Egger M, 2002). SMD calculates effect sizes according to the variance of the sample and assumes differences in variance between trials are a reflection of differences in measurement scales. While there are three commonly used variations of calculating SMD I conduct analyses using the Hedges' adjusted g variation (see Equations 2.8 and 2.9) which incorporate corrections for small sample bias (defined as a comparison between the expected value of a small sample opposed to the expected value of an infinite sample).

Therefore Hedges' adjusted g is calculated by taking the differences in means divided by the pooled variation with an adjustment for small sample bias;

$$g_i = \frac{m_c - m_{Rx}}{S_i}\left(1 - \left(\frac{3}{4N_i - 9}\right)\right) \tag{2.7}$$

With standard error;

$$SE(g_i) = \sqrt{\frac{N_i}{n_{Rx} n_c} + \frac{g_i^2}{2(N_i - 3.94)}} \tag{2.8}$$

Calculating g_i also requires knowledge of the pooled variance which is calculated by;

$$s_i = \sqrt{\frac{(n_{Rx} - 1)SD_{Rx}^2 + (n_c - 1)SD_c^2}{N_i - 2}} \qquad (2.9)$$

Where; m_c = mean in control group
m_{Rx} = mean in treatment group
n_c = number in control group
n_{Rx} = number in treatment group
$N_i = n_{Rx} + n_c$

One issue with using SMD calculations of effect size in practice is that the technique does not alter estimates according to the direction of effect. Therefore, for each comparison I recorded in which direction improvements were associated and effect sizes were adjusted accordingly (i.e. *1 or *-1).

2.4.3 Weighted mean difference models

When combining different studies to gain an overall estimate of effect, it is frequently the case that one desires less contribution from some studies than others (for example estimates of efficacy from smaller populations are likely to be less reliable than those from larger studies and thus I may wish these to have less impact on the overall estimate of efficacy). To address this issue I weighted experiments using the inverse variance method where the greater the variance of effect size estimate, the less weight it is assigned.

I combined individual study estimates in order to calculate the population effect size. Generally speaking, this can be performed by two main methods; fixed and random effects meta-analysis. The choice of technique depends on how much variation is expected across all individual studies. For example, it could be that all experiments represent one 'true' biological effect size, and therefore observed variance represents sampling error. In such a case, then the fixed effects model is the most appropriate because it weights studies with the goal of minimising within study error. In practice, it is more common that studies compared are not identical, due to systematic differences. This variation (or heterogeneity) can be assessed using a random effects model where individual studies are hypothesised to form a normal distribution around a global estimate. Individual effect sizes are first placed into the fixed effects model, which is then used to derive the random effects meta-analysis.

(i) Fixed effects model

In the fixed effects model, individual effect sizes are weighted using the inverse variance method by calculating a weighted average of the treatment effects from the individual trials ((Egger M, 2002), see Equations 2.10 to 2.13).The inverse variance method weights each study by the inverse of the squared variance;

$$Weight_i = \frac{1}{SE^2} \tag{2.10}$$

The effect size (θ_i) is then weighted by;

$$\sum Weight_i \theta_i = Weight * \theta_{IV} \tag{2.11}$$

The effect sizes are pooled, which provides a weighted average of treatment effect for each study estimate;

$$\theta_{IV} = \frac{\sum Weight_i \theta_i}{\sum Weight_i} \tag{2.12}$$

Where θ_i = effect size estimate

And its variance is given by;

$$SE(\theta_{IV}) = \frac{1}{\sqrt{\sum Weight_i}} \tag{2.13}$$

The fixed effects model will give studies with greater variability smaller weights (and thus low influence) whereas in the random effects model the impact of weights is relaxed. We assume in random effects that estimates of effect size form a normal

distribution. The fixed effects model is used to derive the heterogeneity statistic using;

$$Q = \sum \omega_i (\theta_i - \theta_{IV})^2 \qquad (2.14)$$

(ii) Random effects model

As the random effects model assumes study estimates will vary, calculations of effect size differ from the fixed effects model in that they take account of between study variation (τ^2). Thus, in the random effects model, effect sizes (θ_i) are assumed to have a Normal distribution around a global estimate with a variance τ^2. The value of τ^2 is calculated using the DerSimmonian and Laird estimate (DerSimonian and Laird, 1986, Egger M, 2002);

$$\tau^2 = \frac{Q - (k-1)}{\sum Weight_i - \left(\frac{\sum Weight_i}{\sum Weight_i^2} \right)} \qquad (2.15)$$

Where;

Q = Heterogeneity statistic
k = number of comparisons
$Weight_i$ = inverse variance weight

Therefore, if the heterogeneity statistic (Q) is smaller than k-1 (for example if there were no observed variance of effect size) then τ^2 becomes zero and the random effects model, in effect becomes a fixed effects model.

For each study the effect size is weighted incorporating tau by;

$$Weight_i = \frac{1}{SE^2 + \tau^2} \tag{2.16}$$

And the pool effect size is given by;

$$\theta_{DL} = \frac{\sum Weight_i * \theta_i}{\sum Weight_i} \tag{2.17}$$

With standard error;

$$SE(\theta_{IV}) = \frac{1}{\sqrt{\sum Weight_i}} \tag{2.18}$$

And 95 % Confidence limits of;

$$(\theta_{IV}) - 1.96 * SE \quad \text{to} \quad (\theta_{IV}) + 1.96 * SE \tag{2.19}$$

2.4.4 Assessing heterogeneity

For stratified analysis, I assessed whether a particular variable accounts for a significant proportion of the observed heterogeneity. To achieve this I used the Q statistic (which is assumed to follow a χ^2 distribution with k-1 degrees of freedom) under the null hypothesis that the true treatment effect is the same for all trials. The Q statistic examines whether the observed heterogeneity is greater than that expected by chance alone. For continuous independent variables (e.g. age at treatment, duration of treatment) I defined strata using inter-quartile ranges to establish four groups within the variable of interest. To account for the number of comparisons I adjusted our critical value using Bonferroni correction (see Section 2.4.5).

2.4.5 Bonferroni corrected p values

While exploring datasets and generating hypotheses it is an expectation that each individual dataset may be used multiple times for each hypothesis tested. While a critical p value (termed "α value") of 0.05 may be appropriate for a given individual analysis, multiple comparisons increase the likelihood of false positives. One way to account for this systematically is to use Bonferroni correction (see Equation 2.20). This methodology decreases the alpha value (and therefore the likelihood of reaching statistical significance decreases) as the number of comparisons increase.

$$\alpha = 1 - 0.95^{\frac{1}{n}} \qquad (2.20)$$

Where: n= number of comparisons

Thus the null hypothesis (that there is no statistical difference between groups) can only be rejected where $p < \alpha$. As I planned multiple analyses across different variables and datasets, α values which can be found stated in tables and within the main body of the text. Figure 2.2 illustrates how the equation works in practice.

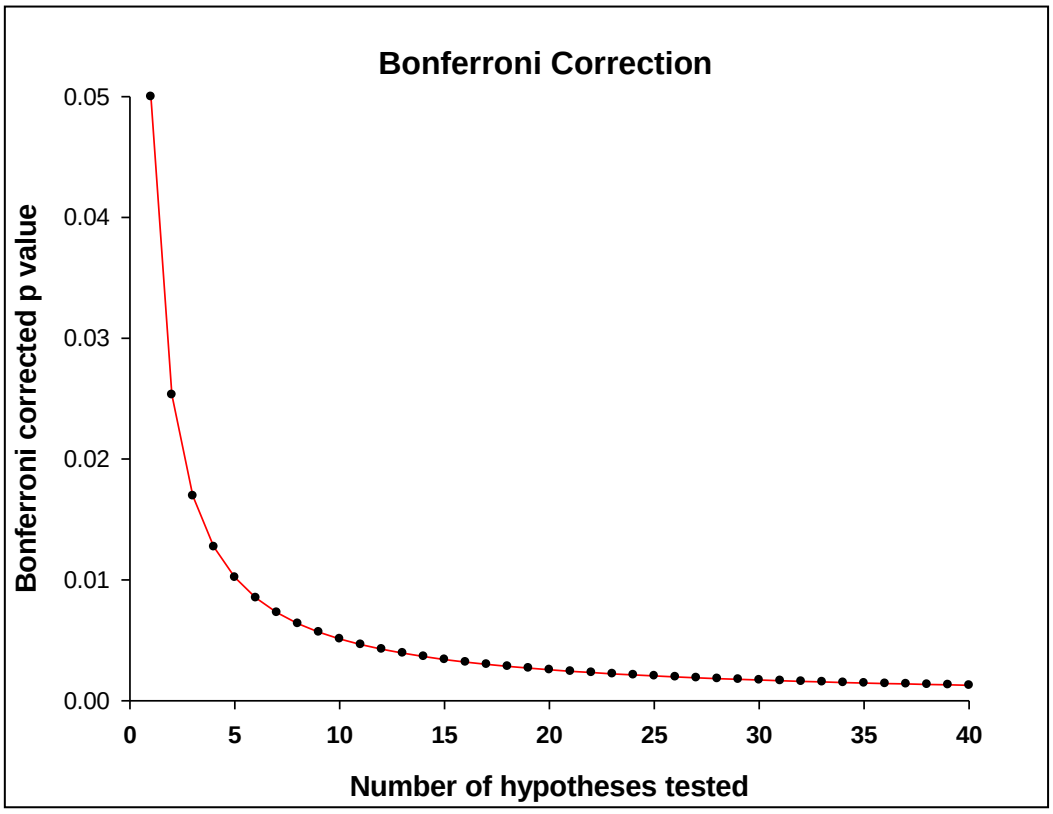


Figure 2.2: The Bonferroni correction corrects the α level according to the number of hypotheses tested. The critical value of p for significance (α level on y axis) becomes more stringent as the number of comparisons made increases (x axis). Multiple values of α will be used across the work conducted**.**

2.4.6 Meta-regression

Meta-regression is an alternative method of assessing the impact of particular study covariates by examining statistical heterogeneity. Meta-regression has particular advantages over stratified meta-analysis in the respect that it accounts for both between and within study variation and it is possible to enter more than one covariate into the model. However, the sensitivity of the approach is likely to differ from stratified meta-analysis. As there is currently no consensus on which technique is most suitable for our given datasets I prespecified that I would use stratified techniques for primary analysis whereas meta-regression techniques (performed using STATA version 10) were used to investigate relationships both between and within outcomes.

Similar to stratified meta-analysis, meta-regression uses individual effect sizes to derive summary data which are weighted by the inverse variance method previously described. There are a number of key differences from stratified meta-analysis; variables are assessed for their ability to fit a linear regression model, data are not required to be stratified and the heterogeneity unit of interest is τ (see 2.14 above). Our use of meta-regression is strictly limited to investigating relationships within and between outcome measures. As the effect size estimates are continuous variables these do not need to be modified further before entering the model.

For meta-regression analyses STATA outputs provide information regarding the number of studies, tau squared, I squared and the adjusted R^2. The value of the adjusted R^2 represents the strength of the relationship between the variance in a covariate of interest and variance in effect size.

Uni-variate meta-analysis

Where I examined the impact of one variable on another I used uni-variate meta-regression. Uni-variate meta-regression analyses were performed to inspect the impact a single dependent variable had on the observed independent effect size. The following command was used to investigate both relationships between outcomes using STATA

$$\text{Metareg } Q_{DV}\ Q_{IV}, \text{WSSE } (SE_{DV}) \qquad (2.22)$$

Where;

Q_{DV} =Effect size of dependent variable

Q_{IV} = Effect size of independent variable

SE_{DV}= Standard error of the effect size of dependent variable

2.4.7 Interpreting meta-regression analyses

Where I performed simple linear meta-regression I used adjusted R^2 values to identify how much of the variance in the dependent variable can be explained by the independent variable. The adjusted R^2 represents the proportion of between study variance (τ) which can be explained by covariates and is calculated by;

$$\text{Adjusted } R^2 = \frac{\tau^2_{nocovariates} - \tau^2_{withcovariates}}{\tau^2_{nocovariate}} \quad (2.23)$$

Similar to linear regression, it is possible for the R^2 value to be negative in the circumstance where covariates explain less of the heterogeneity than would be expected by chance. The significance level of meta-regression analyses was adjusted using α values calculated using Bonferroni corrections, as shown in 2.20.

2.5 Assessing publication bias

The identification of missing negative or neutral studies is assessed using three different techniques: Egger regression (Egger et al., 1997), funnel plots and Trim and Fill models (Duval and Tweedie, 2000). For inputting data into such models, where more than one outcome was measured in a single cohort of animals I used all of these outcomes in the publication bias analysis, rather than the summary outcome data for each cohort used in the meta-analysis. Therefore I took estimates of effect size within pre-nested data.

It should be stressed that while these analyses are designed to asses publication bias it could be that this is suggested from analyses due to other reasons. For example, it could be that studies were methodologically different from larger ones, or that the disparity could be explained because only the best interventions are taken forward at each stage of drug discovery.

2.5.1 Egger regression

Egger regression works under the principle that smaller studies have increased random error and are therefore likely to have a greater variance around the mean. To perform Egger regression one must plot effect size divided by the standard error on the Y-axis which is plotted against precision (inverse of the variance) on the X-axis. If the intercept of the regression line and its 95% confidence limits do not cross the origin then this indicates a presence of publication bias.

2.5.2 Funnel plot

Funnel plots are scatterplots designed to allow the visual assessment of publication bias through plotting calculated effect sizes against precision (the inverse of the variance for individual studies). Small studies generally have greater variance and tend to scatter widely at the bottom of the graph whereas large studies form a much narrower distribution of effect size. If a given dataset has no publication bias, the data should form a symmetrical inverted 'funnel' shape with its line of symmetry centred on the global estimate of efficacy. For publication bias to exist, I may expect a number missing imprecise studies with negative or neutral effect sizes.

2.5.3 Trim and fill

While the funnel plot can be used for visual assessment of publication bias, there are a number of notable weaknesses: interpretation is subjective and there is no way of quantifying missing studies. To address such issues 'Trim and fill' is a particularly useful technique which uses an iterative method to identify hypothetically missing studies (Duval and Tweedie, 2000). If publication bias was found within datasets, Trim and Fill methods would compare the right hand side of the funnel plot to the left hand side and calculate the number of asymmetrical studies (k0, see Figure 3.3). Those studies on the right hand side which are asymmetrical are trimmed until there are only symmetrical studies left and the 'true' pooled effect size is calculated. Those studies which were removed and their missing counterparts (on the left hand

side of funnel plot) are replaced until the pooled effect size stabilises (Peters et al., 2007).

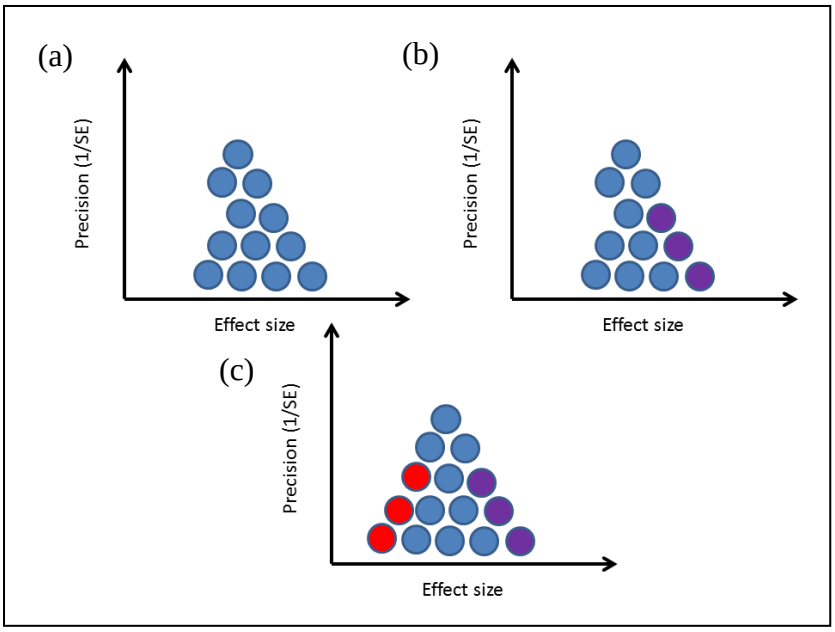


Figure 2.3: Trim and fill estimates were used to quantify the number of missing studies. (a), (b)The methodology 'trims' asymmetrical studies within funnel plots (where effect size is plotted against precision, asymmetry shown in purple). (c) The process then adds missing studies on the left hand side (in red) and recalculates the pooled estimate. This process is repeated until the pooled effect size stabilises.

Chapter 3: Systematic Search Results; describing the literature and planning meta-analyses

A systematic search provides an unbiased, comprehensive collection of published literature. Collating studies of interventions tested in transgenic mouse models has a number of key advantages: (1) to consolidate understanding of how we assess efficacy in animal models; (2) to help identify gaps in our knowledge; and (3) to plan effective meta-analysis. Thus, this chapter describes the literature on transgenic mouse models of Alzheimer's disease through outcomes, models, interventions and study quality.

3.1 Systematic search results

From our initial search, I identified 8360 publications. From these, we (MM and KE) identified 427 publications where a single intervention was tested in a transgenic mouse model (see Figure 3.1 for flow diagram). I identified that since 1998 there has been an increase in the number of publications per year testing interventions in transgenic mouse models of Alzheimer's disease (Figure 3.2). Five publications were excluded because I did not consider the SAMP8 mouse a specific model of AD.

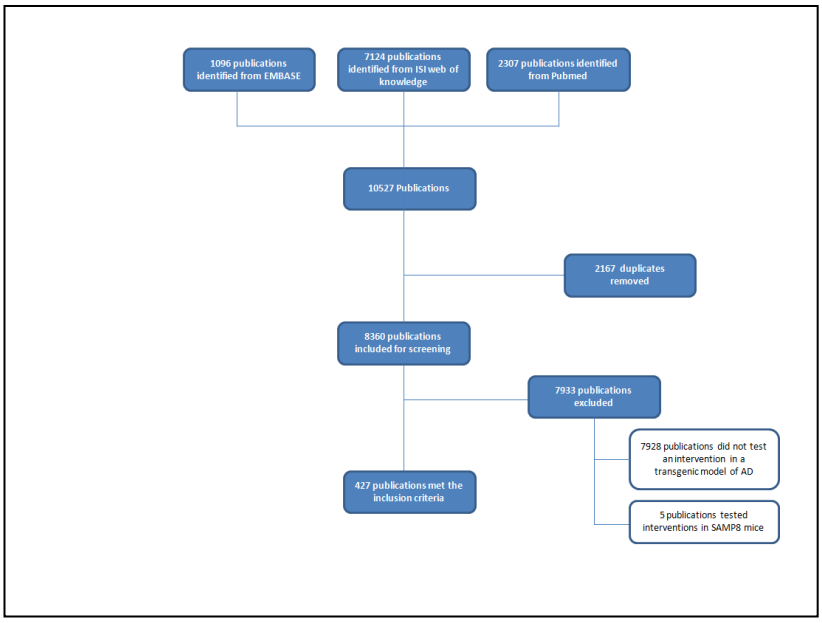


Figure 3.1: Publications were identified from systematic search were screened for possible inclusion. A notable exclusion the systematic search was the Senescence Accelerated (SAMP8) mouse.

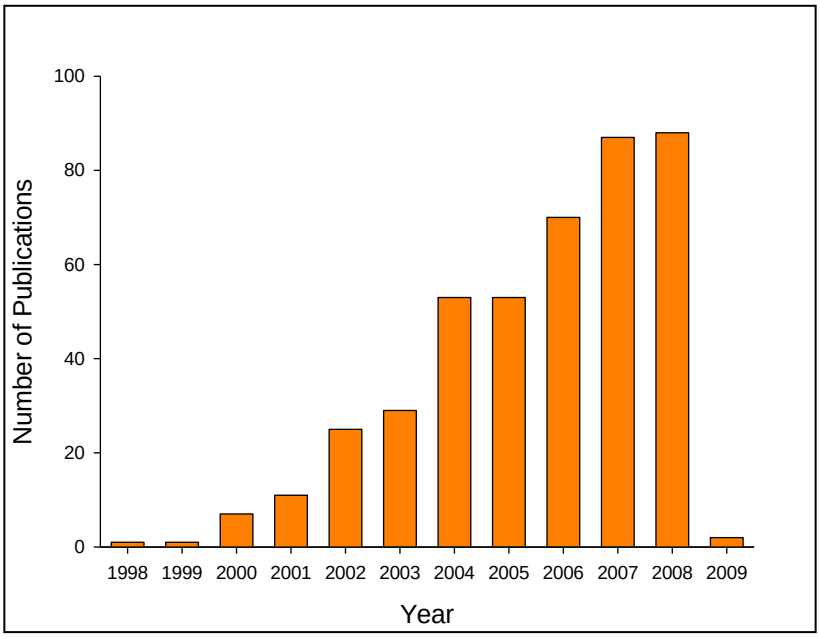


Figure 3.2: The search results identified that there has been an increase in the total number of publications reporting the testing of interventions in transgenic mouse model of Alzheimer's disease since 1998.

3.2 Summary of outcome measures

From 427 publications, I identified six main pathological outcome measures (amyloid plaque burden, amyloid beta 40, amyloid beta 42, tau, cell infiltrates and neurodegeneration (See Figure 3.3) alongside neurobehavioural outcomes (Figure 3.4).

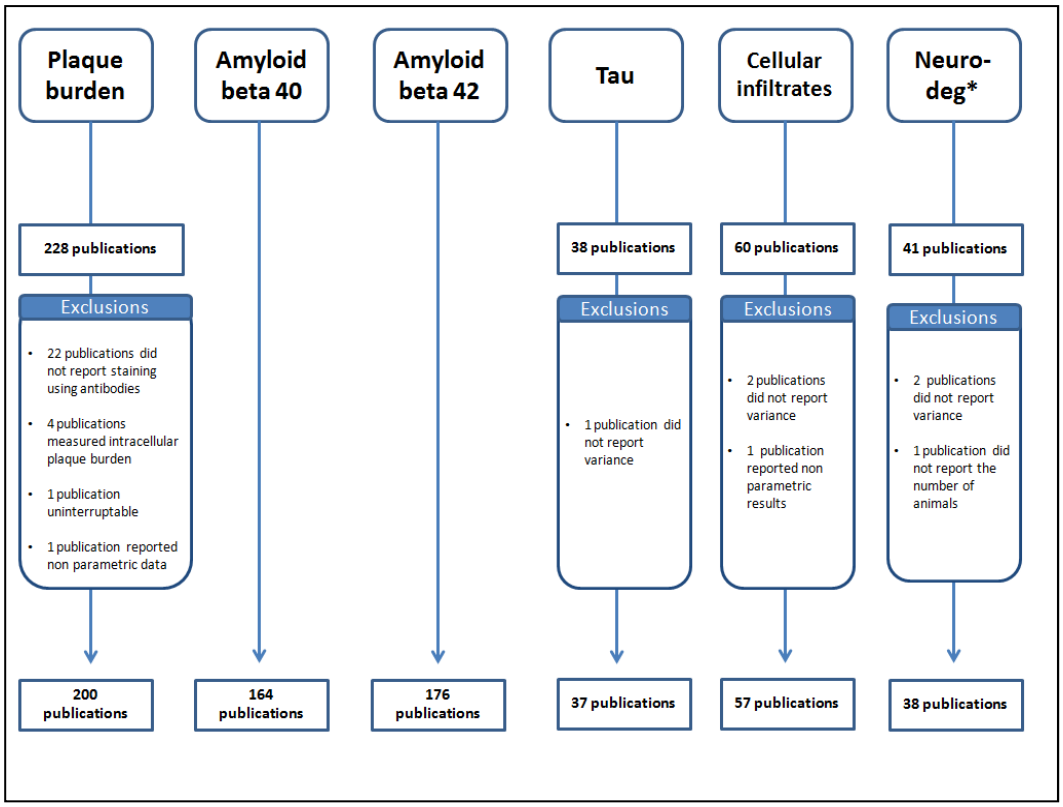


Figure 3.3: From 427 publications I identified a number of main pathological outcomes including, plaque burden, amyloid beta 40, amyloid beta 42, tau, cell infiltrates and neurodegeneration (Neurodeg*). The number of publications reported each of these outcomes is reported alongside the details of publications excluded. See methods for further details of data inclusion.

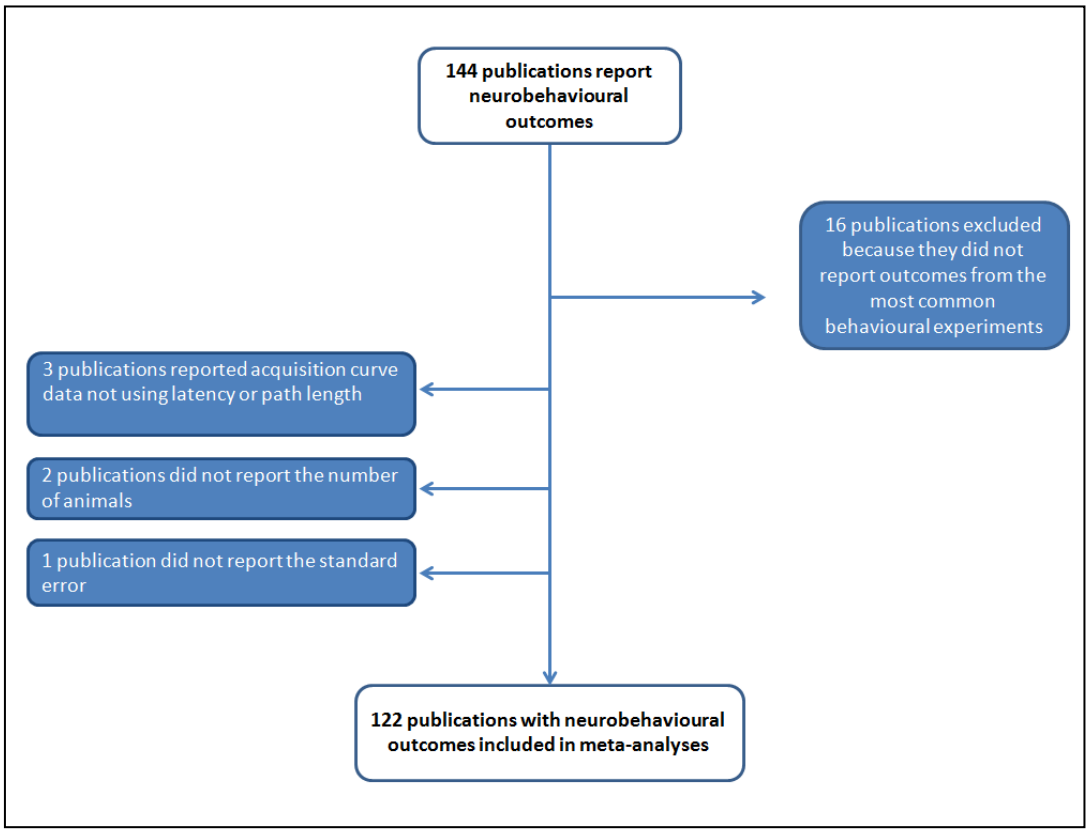


Figure 3.4: From 427 publications I identified 144 publications which reported neurobehavioural outcomes. Of these, 122 publications were taken forward to meta-analysis stage and the number of excluded publications is explained above. See methods for details regarding extraction of MWM acquisition data and see Figure 3.12 for neurobehavioural paridigms included.

3.3 Pathological outcome measures

3.3.1 Plaque burden

Amyloid plaque was the most commonly reported outcome found in 53% (228/427) of publications, representing 5613 mice. Over 90% of experiments were quantified using immunohistochemical methods (using antibodies such as a 6E10 or 4G8). To a lesser extent, Congo red (8.9%) and Thioflavin S (15.2%) staining techniques were also used (see Figure 3.5 for overview). In summary, sufficient data were available for reliable estimates of efficacy for each staining method and to investigate associations between immunohistochemistry and congo red, and immunohistochemistry and Thioflavin S.

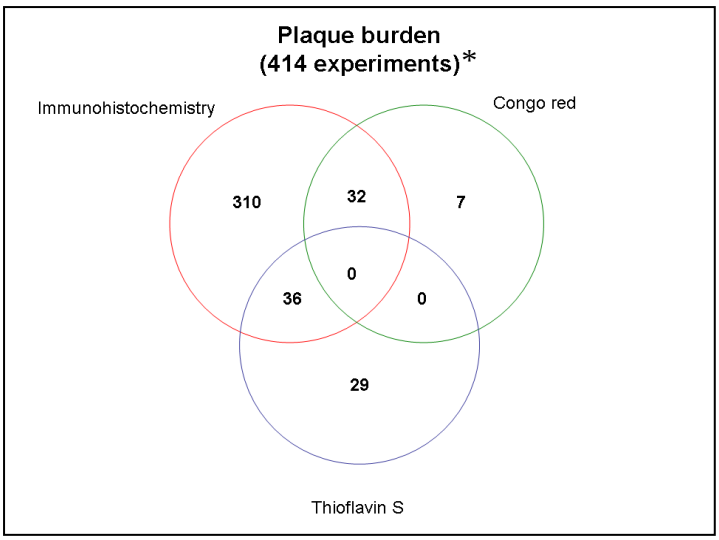


Figure 3.5: 414 experiments were identified which quantified changes in plaques. The number of experiments using immunohistochemistry, congo red and thioflavin S can be found in each respective circle. Those cohorts where more than one technique was used can be found where circles overlap. *NB for calarity these estimates do not include those experiments where less than 3.5 animals exist as these could not be used in analyses.

3.3.2 Amyloid beta species

Overall, 202 publications reported amyloid beta species representing 6545 animals and 475 experiments. Of these, 177 publications (88%) report amyloid beta 42 levels, 165 (82%) report amyloid beta 40 levels and 37 publications report total amyloid beta (see Figure 3.6 for number of experiments). As both monomer, oligomer and trimer species of amyloid all represented specific amyloid aggregates I combined such data for exploratory analyses (Table 3.1 for summary and Section 4.2 for analyses). The most prominently used immunoassay technique was the ELISA; used in 90% (187/208) of publications. The methodology of the ELISA was considerably variable (e.g. solutes used) but I did not quantify this in further detail.

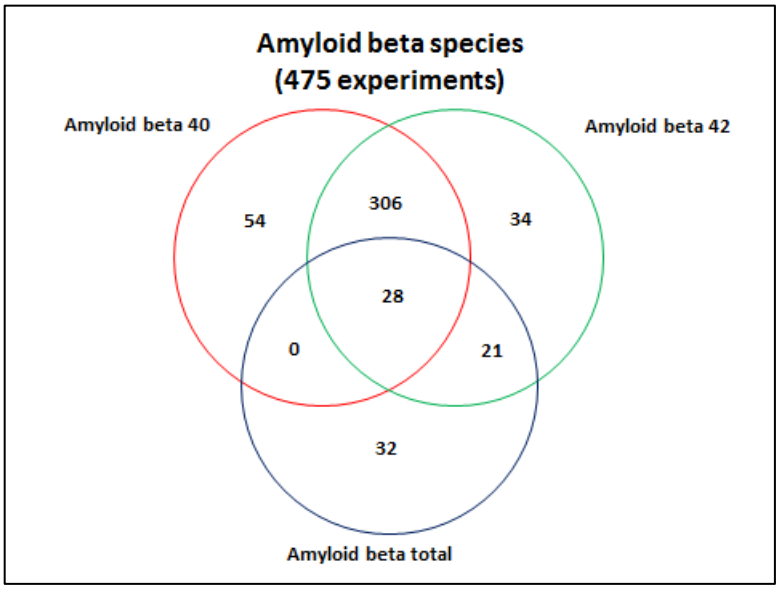


Figure 3.6: 475 experiments were identified which quantified changes in amyloid. The number of experiments assessing amyloid beta 40, amyloid beta 42 and total amyloid beta can be found in each respective circle. Those cohorts where more than one technique was used can be found where circles overlap.

Amyloid species	Specificity	Solubility	Total number of experiments
Oligomer	Non specific	soluble	17
		Unknown	14
	6-mer	soluble	2
	3-mer	soluble	3
	3-mer	unknown	1
	12-mer	soluble	1
	24-mer	soluble	1
	4-mer	soluble	1
	9-mer	soluble	1
	Ab*56	soluble	1
	40-mer	soluble	1
		Unknown	1
Monomer	Non specific	soluble	1
		Unknown	2
	Monomers &dimers	Unknown	1
Total			48

Table 3.1: Amyloid aggregates were assessed in a number of different methods including the specific amyloid aggregate assessed and species solubility.

Solubility of amyloid species

Within each of the main amyloid outcomes (amyloid beta 40, amyloid beta 42 and total amyloid beta) I quantified the solubility of amyloid species wherever possible (Figure 3.7). Of the 388 experiments which examined amyloid beta 40, 276 stated solubility, most commonly examining both soluble and insoluble species. For amyloid beta 42, 295 of 389 experiments reported solubility where again experiments most frequently recorded both soluble and insoluble species. For total amyloid 60 experiments reported the solubility of amyloid species where the 'total' amyloid was the most frequently reported.

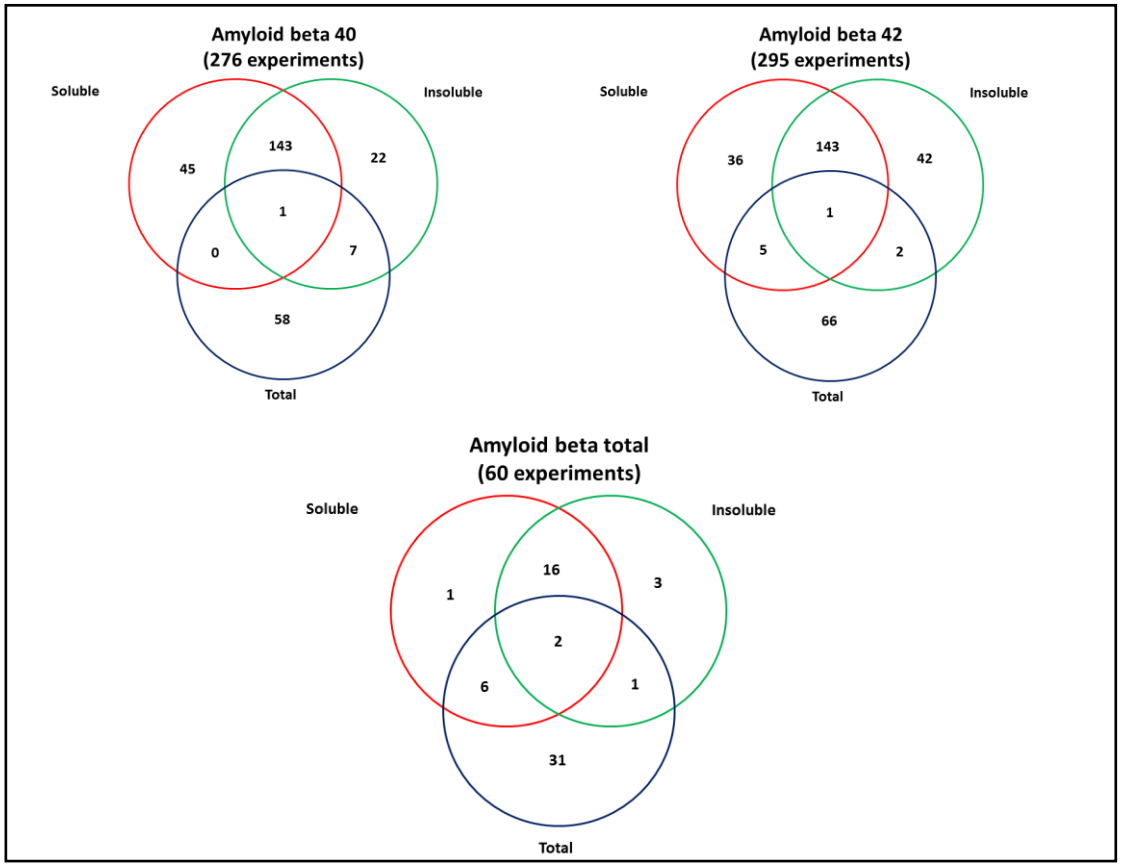


Figure 3.7: The number of experiments which reported the solubility of each of the main amyloid beta outcomes (amyloid beta 40, amyloid beta 42 and amyloid beta total) is summarised in Venn diagrams. Totals differ from those stated previously as data were only included if they stated solubility.

3.3.3 Tau

Intracellular neurofibrillary tangles were reported in 38 publications, representing 84 experiments and 984 animals. The extent of tau pathology was quantified by both the phosphorylation state of tau (59 publications) and the overall levels of tau (53 experiments, Figure 3.8). Within such categories, there was substantial methodological heterogeneity (see Figure 3.9 for phosphorylation antibodies identified). Both overall levels of tau and phosphorylation levels provide different assessment techniques for tau abnormalities in AD. Therefore, I grouped each of these together for overall analyses, and 28 comparisons could be used to examine whether changes in tau could explain changes phosphorylation state.

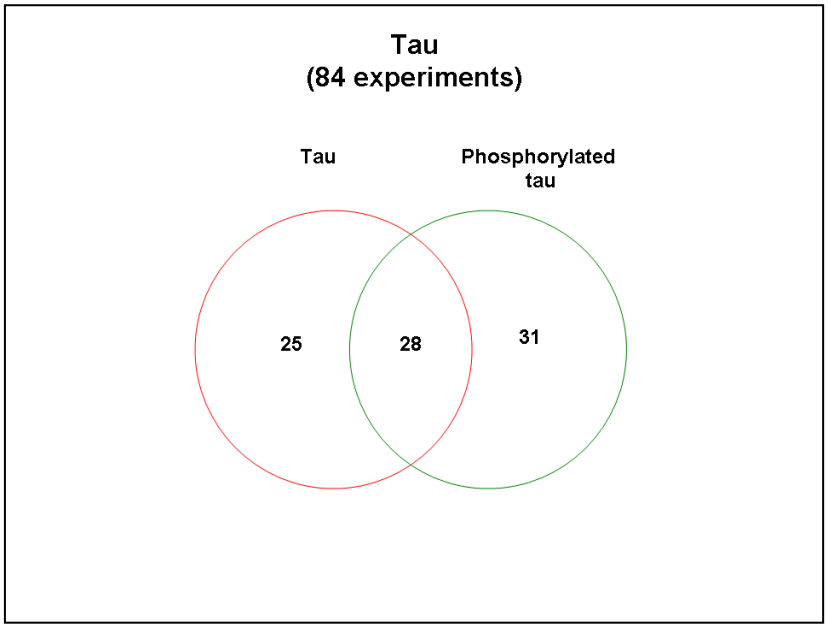


Figure 3.8: 84 experiments were identified which quantified changes in tau. The number of experiments assessing overall tau and the phosphorylation state of tau can be found in each respective circle. Those cohorts where more than one technique was used can be found where circles overlap.

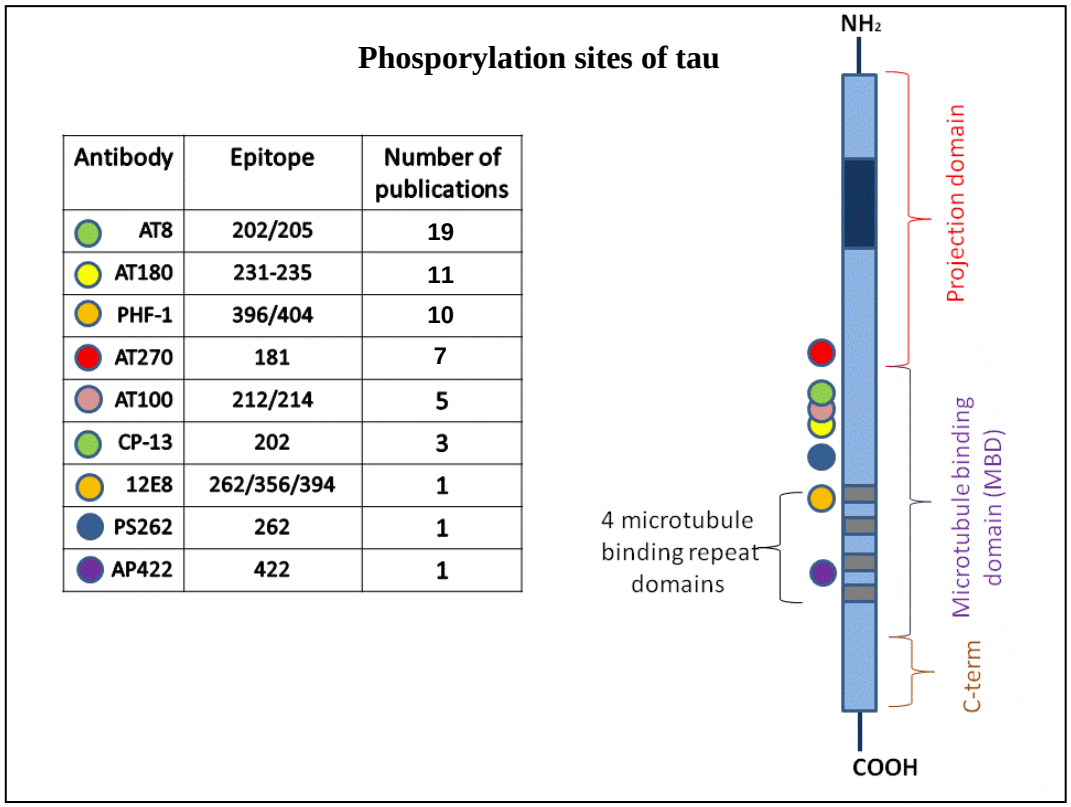


Figure 3.9: A number of different phosphorylation sites for tau were described in the literature. The antibody used, and the epitope target alongside the number of publications using each staining technique are described.

3.3.4 Cell infiltrates

Astrocytosis was reported in 36 publications (representing 43 cohorts, 633 animals) and was almost universally (34 publications) stained using Glial fibrillary acidic protein (GFAP). Microgliosis was reported in 46 publications (representing 82 cohorts and 823 animals) most commonly stained with CD45 (see Table 3.2 for breakdown of staining techniques used).

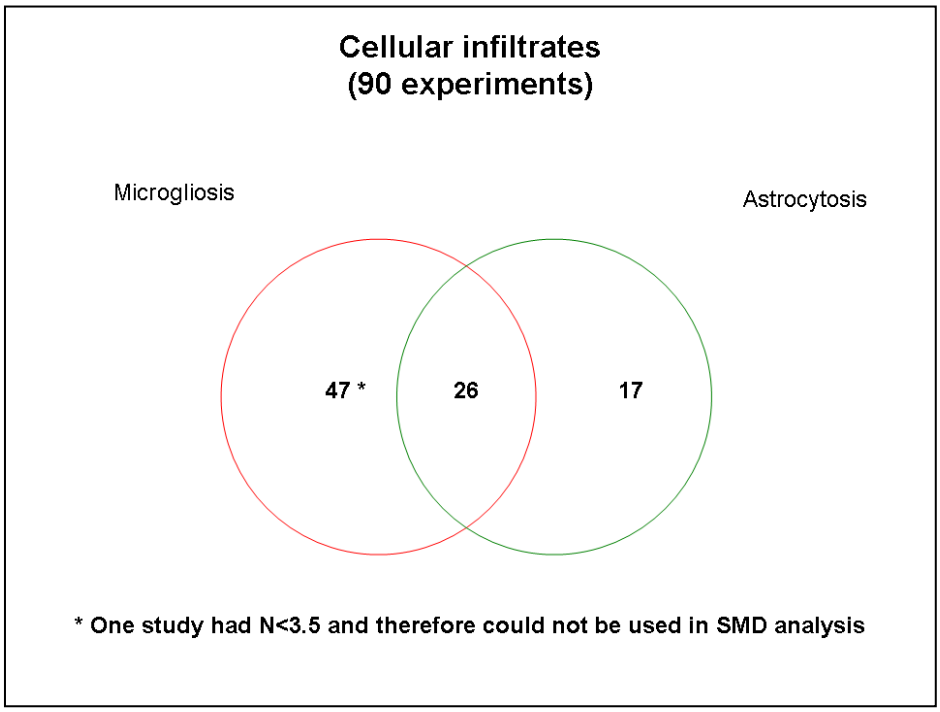


Figure 3.10: 90 experiments were identified which quantified changes in cellular infiltrates. The number of experiments assessing microgliosis and the astrocytosis can be found in each respective circle. Those cohorts where more than one technique was used can be found where circles overlap.

Antibody/Staining technique used	Number of publications
CD45	16
Cd11b	7
Fcγ-R	5
Iba-1	5
MHC-ii	5
CD-68	3
F4/80	3
CD11	2
CD40+	2
Lectin	2
SRA	2
B4	1
c11b	1
CD45:plaques	1
CR3	1
Phosphotyrosine	1
IA/IE	1
IB4+	1
MAC-3	1
Macrosialin	1
PT-stained	1
Tomato-lectin staining	1
unknown	1
F4/80	1
cd3	1

Continued

Table 3.2: Various antibodies and staining techniques were used to describe microglia. Table describes such data; the most common of which was CD45 antibody staining.

3.3.5 Neurodegeneration

Outcome measures of neurodegeneration were reported in 41 publications representing 64 experiments and 958 animals. Measures of neurodegeneration were represented by a continuum of impaired cell and synapse functionality and cell death. Data regarding all potential outcome measures of neurodegeneration were captured which included measures of neurogenesis with the interpretation that down regulation of neurogenesis is a feature of the global neurodegeneration present. Figure 3.11 summaries the number of publications which measured direct or indirect measures whereas Table 3.3 explains the abundance of each direct (e.g. an actual measure of neuronal loss) and indirect (e.g. cell signalling or DNA fragmentation).

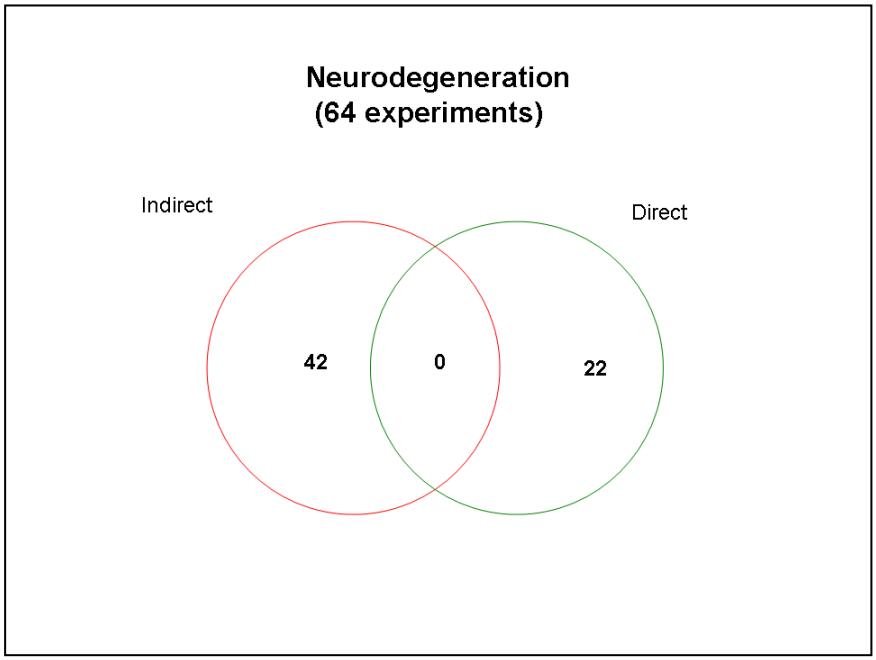


Figure 3.11: 64 experiments were identified which quantified changes in neurodegeneration. The number of experiments assessing overall direct and indirect measures can be found in each respective circle. Those cohorts where more than one technique was used can be found where circles overlap.

Mode	Outcome measure	Number of publications
Indirect	Synaptophysin staining	26
	BrdU Neurogenesis	9
	DCX Neurogenesis	5
	Caspase-3	4
	Bax proteins	3
	DNA fragmentation	3
	Synaptic density	3
	Calretinin-positive cells	2
	SNAP-25	2
	AchR	1
	BrdU/GFAP	1
	BrdU/NeuN	1
	Caspase 9	1
	Cytochrome C	1
	Dynamin-1	1
	GABAA receptor a1 subunit	1
	NeuN Neurogenesis	1
	Neuogenesis BrdU/NeuN	1
	Neurogenesis	1
	NR2B subunit	1
	Par-4	1
	p-NR2B subunit	1
	pNR2B/NR2B	1
	PSD-95	1
	Ubiquitin-positive particles	1
Total indirect		**73**
Direct	Neuritic dystrophy	7
	Axonal degeneration	6
	Apoptotic neurons	3
	Degenerating Neurons	3
	Neuronal count	3
	Synapse number	3
	Curvature ratio	1
	Dystrophy size	1
	Fluoro Jade	1
	Mean number of dystrophic neurites	1
	Mean total area of dystrophic neurites	1
	Apoptotic count	1
Total direct		**31**

Table 3.3: Both direct and indirect measures were of interest for neurodegeneration outcomes. Indirect measures were more frequently identified opposed to direct ones, of which the most commonly reported outcome of interest was synaptophysin.

3.3.6 Pathological outcomes by brain region

For each pathological outcome extracted additional details were also captured regarding the specific brain region assessed. The most commonly assessed brain regions were the hippocampus (422 experiments) and the cortex (390 experiments). Table 3.4 summarises the specific brain regions used in experiments across all five pathological outcome measures of interest.

	Amyloid beta 40	Amyloid beta 42	Cellular infiltrates	Neurodegeneration	Plaque area	Tau
Amygdala	n.d.	n.d.	n.d.	n.d.	3	6
Brain	266	251	24	25	163	38
Brainstem	n.d.	n.d.	n.d.	n.d.	n.d.	6
Cerebellum	2	3	n.d.	n.d.	n.d.	n.d.
Cingulate gyrus	n.d.	n.d.	n.d.	n.d.	2	n.d.
Cortex	82	81	42	23	162	9
Forebrain	9	12	n.d.	n.d.	2	n.d.
Frontal lobe	n.d.	n.d.	n.d.	n.d.	1	n.d.
Frontal section	n.d.	n.d.	n.d.	n.d.	1	n.d.
Hippocampus	65	81	50	30	196	42
Olfactory tract	n.d.	n.d.	n.d.	n.d.	1	n.d.
Parietal lobe	n.d.	n.d.	n.d.	n.d.	1	n.d.
Spinal cord	n.d.	n.d.	n.d.	1	n.d.	10
Spinal ventral roots	n.d.	n.d.	n.d.	2	n.d.	n.d.
Striatum	1	n.d.	n.d.	n.d.	n.d.	n.d.
Subiculum	n.d.	n.d.	1	n.d.	n.d.	n.d.
Thalamus	n.d.	n.d.	1	1	n.d.	n.d.
Ventricles of walls	n.d.	n.d.	n.d.	1	n.d.	n.d.
Totals	**425**	**428**	**118**	**83**	**532**	**111**

Table 3.4: The specific brain regions used for experiments are shown across all five pathological outcome measures. A single cohort may be represented numerous times (n.d. no data)

3.4 Neurobehavioural paradigms

144 out of 427 publications (33.7%) reported neurobehavioural outcomes. In total, thirty different neurobehavioural paradigms were described within the literature; of which the MWM was the most frequently used (83 publications). Table 3.6 summarises the frequency of behavioural paradigms most commonly used. Methodological variations extended to apparatus used, conduct and choice of outcomes assessed. I planned to take forward data for individual paradigm analyses wherever paradigms featured in ten or more publications (Figure 3.12 for summary). While this was possible for data from the MWM, RAWM, fear conditioning, Novel object recognition task (NORT) and Y/T maze there were continuity issues with direction of effect for the open field test which are explained (Section 3.4.6).

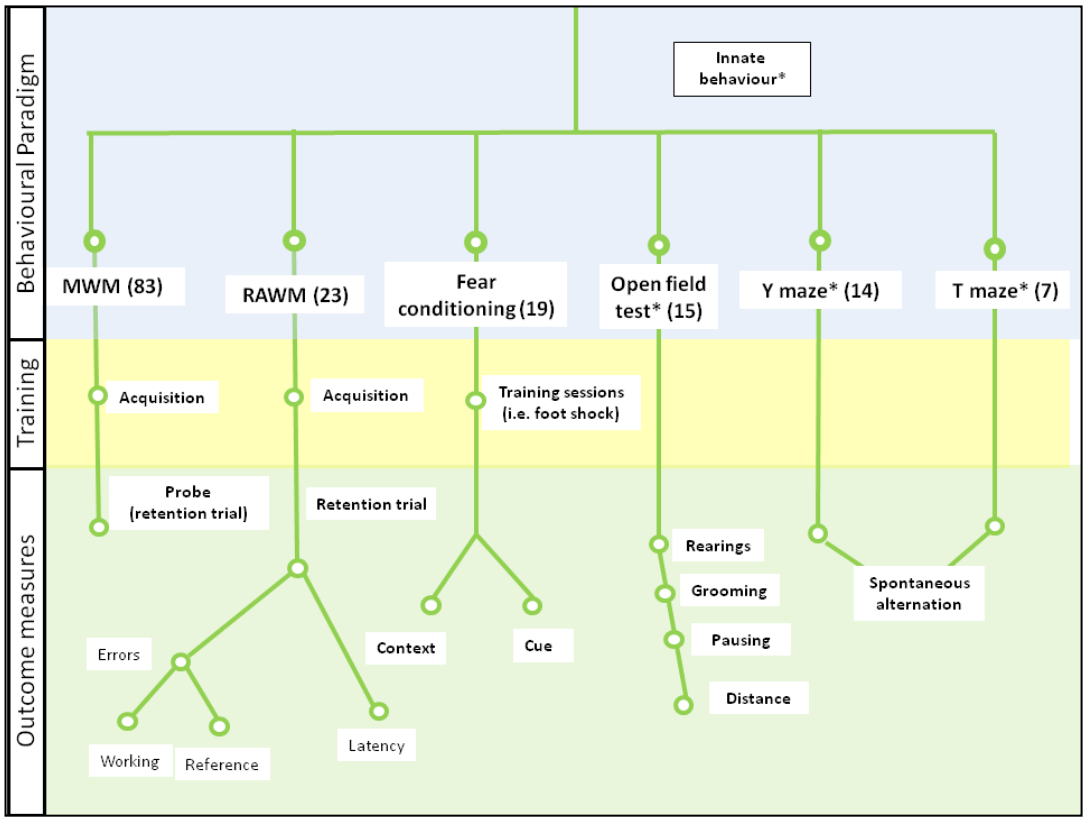


Figure 3.12: The six most commonly used behavioural paradigms and number of publications (in brackets) were the Morris water maze (MWM), Radial arm water maze (RAWM), Fear conditioning, open field test, Y-maze and T-maze. A number of paradigms are based solely on innate behaviour (*), whereas others require training.

3.4.1 Morris water maze

The MWM was the most commonly used behavioural paradigm, and outcomes were reported from 83 publications. More specifically, this included 130 control and treatment acquisition curves (2151 animals) and 113 experiments from the probe phase (2018 animals).

(i) Acquisition phase of the Morris water maze

Methods of quantification within the acquisition phase included 'latency' (107 experiments), 'path length' (57 experiments), 'trials to criterion' (2 publications), 'search error' (2 experiments) 'cumulative distance to platform' (1 experiment) 'time in outer zone' (1 experiment) and 'difference in path length' (1 experiment).

I observed that the methodology of studies described was highly variable; including parameters such as the temperature of water used (temperatures ranged from 16 to 28 °C), the size of the pool (85 to 200 cm), number of trials per day (2 to 12) and number of days training (1 to 15). See figure 3.14.

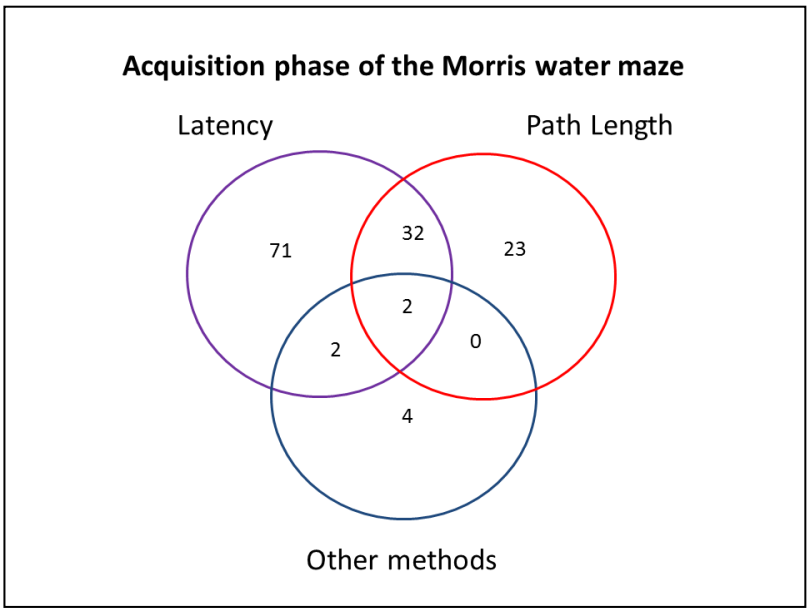


Figure 3.13 (previous page): Outcomes commonly reported from the Morris water maze were predominantly 'latency' and 'path length'. Other methods included difference in path length, time in outer zone, search error and trials to criterion.

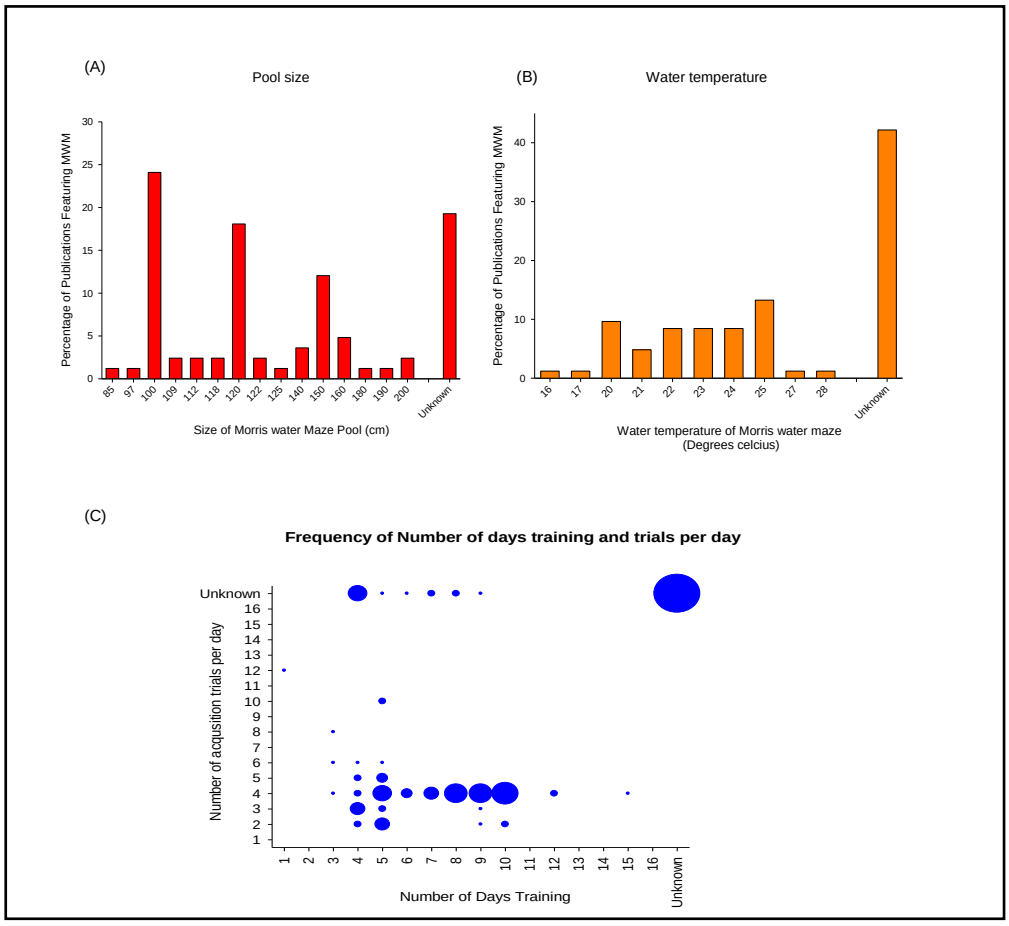


Figure 3.14: The use of the Morris water maze (MWM) varied considerably with respect the size of the pool used (A), water temperature (B), the number of training trials per day and number of days trained (C). For figure C symbol size represents the number of experiments.

(ii) Probe phase of the Morris water maze

The probe phase was also extremely variable in its use. Twelve principle methods were used for illustrating efficacy and within the 57 studies which used the probe phase of the MWM there were 59 different approaches used to demonstrate efficacy (See Table 2 and Table Legend for details). Such methodological heterogeneity would be the focus of subsequent meta-analysis techniques.

Method of probe assessment	Trials to criterion	Multiple probe trials	<24 hours	>24 hours	Total number of seconds	Number of publications
Time in target quadrant	no	no	no	yes	31 to 60 61 to 120 unknown	13 3 2
			yes	no	31 to 60 61 to 120	6 2
			unknown	unknown	31 to 60 61 to 120 unknown	2 1 2
			Yes *	no	31 to 60	1
		yes	no	yes	31 to 60	1
			yes	no	31 to 60 unknown	2 1
				yes	31 to 60	1
			no	yes	31 to 60	1
			Yes *	no	0 to 30 31 to 60	1 2
	yes	no	no	yes	31 to 60	2
		yes	yes	yes	31 to 60	1
Time in target quadrant Total						**44**
Number of platform crosses	no	no	no	yes	31 to 60 61 to 120 unknown	7 3 1
			yes	no	31 to 60 61 to 120 unknown	2 1 1
			unknown	unknown	61 to 120	1
		yes	Yes *	no	31 to 60	1
				yes	31 to 60	1
	yes	yes	yes	yes	31 to 60 unknown	2 2
Number of platform crosses Total						**22**
Speed	no	no	no	yes	31 to 60 61 to 120 unknown	2 1 1
			yes	no	31 to 60	1
		yes	no	yes	31 to 60	1
			yes	no	31 to 60	2
			Yes *	no	0 to 30 31 to 60	1 1
Speed Total						**10**
Latency to cross platform	no	no	no	yes	31 to 60	1
		yes	no	yes	31 to 60	1
			yes	no	31 to 60	1
	yes	yes	yes	yes	31 to 60 unknown	4 2
Latency to cross platform Total						**9**
Distance travelled to platform[1]	no	no	no	yes	31 to 60 61 to 120	1 2
		yes	no	yes	31 to 60	1
			yes	no	31 to 60	1
Distance travelled to platform Total						**5**
Number of entries to target quadrant	no	no	no	yes	unknown	1
			unknown	unknown	unknown	1
		yes	yes	no	unknown	1
	yes	yes	yes	yes	31 to 60	1
Number of entries to target quadrant Total						**4**
Distance travelled in target quadrant	no	no	no	yes	31 to 60	1
			yes	no	31 to 60	1
		yes	yes	yes	31 to 60	1
Distance travelled in target quadrant Total						**3**
Number of entries to target zone	no	no	no	yes	61 to 120 unknown	1 1
Number of entries to target zone Total						**2**
Average distance to platform	yes	no	no	yes	31 to 60	2
Average distance to platform Total						**2**
Time at platform	no	no	no	yes	61 to 120	1
Time at platform Total						**1**
Time in target zone	no	no	no	yes	61 to 120	1
Time in target zone Total						**1**
Search Ratio	yes	no	no	yes	31 to 60	1
Search Ratio Total						**1**

Table 3.5 (previous page): 12 principle methods were used to assess Morris water maze probe performance. Within these assessments studies varied by whether they; trained the mice to criterion, preformed multiple trials, assessed probe performance less than (<24) or greater than (>24) 24 hours after training, and the total number of seconds.

3.4.2 Fear conditioning

Contextual and cued fear conditioning provide a classic example of Pavlovian associative learning and the paradigm was used in 19 publications (45 experiments). The test typically trains mice to associate an auditory cue with a paired electric shock, and then tests mice for their contextual freezing ability after initial training sessions (Contextual behaviour assessed in 19 publications, see Table 3.5 for more details). Frequently, cued fear conditioning is also assessed (7 publications) where the environment changes but an original cue for the stressor (e.g. auditory cue is used once more).

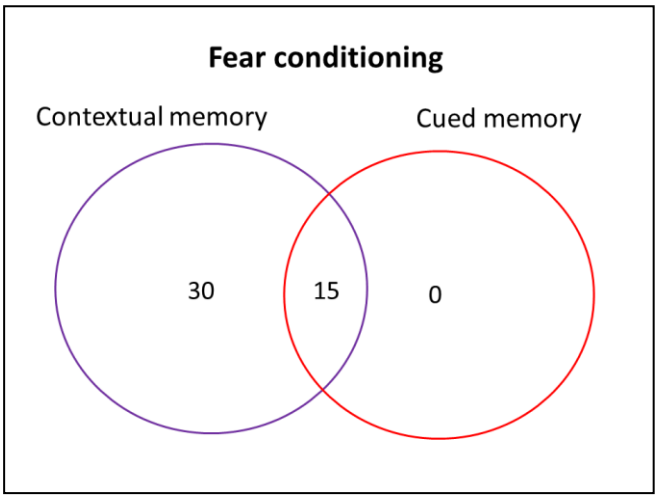


Figure 3.15: Outcome from the Fear conditioning paradigm were described as contextual or cued memory assessments. Number shown describe the number of experiments which perform each.

3.4.3 Radial arm water maze

The radial RAWM was used in 23 publications, however as one publication did not state error on data I only describe 22 publications in summary statistics.

Use of the RAWM is considerably varied and I identified different uses where arms were baited with food or had a hidden platform. Hidden platform constructs featured in 25 experiments, whereas baited arm experiments featured in 7 (Figure 3.16).

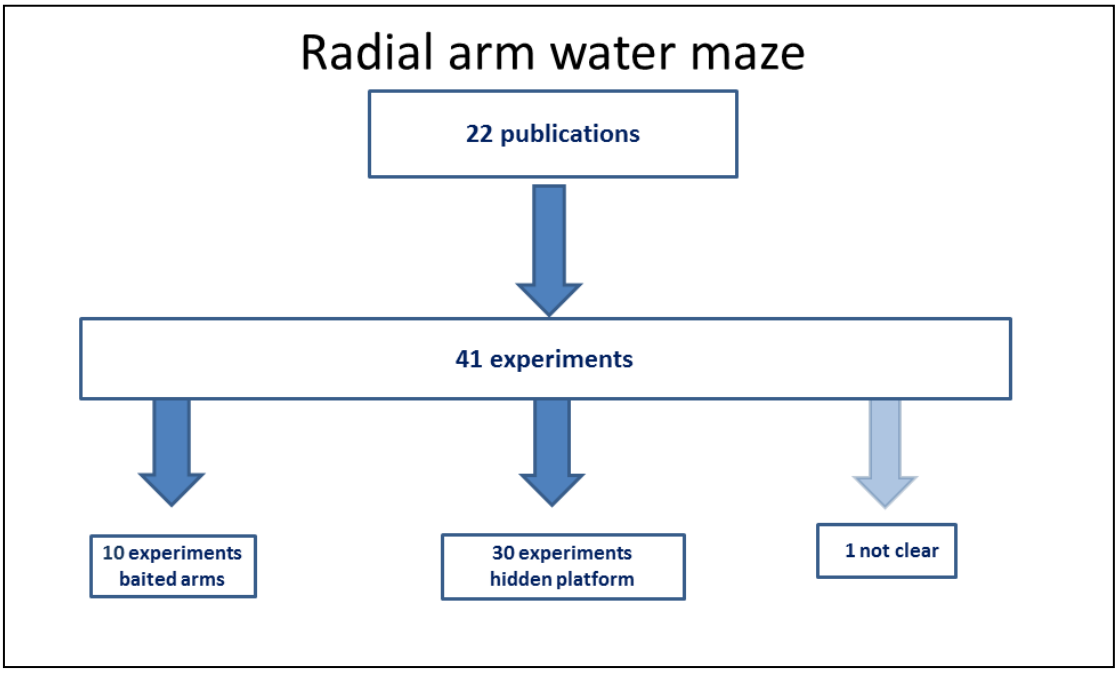


Figure 3.16: The Radial arm water maze has two principal forms, baited and hidden arm constructs. For one experiment it was not clear which methodology was used.

3.4.4 T-maze & Y-maze

The T and Y maze were used in 7 (11 experiments) and 14 (17 experiments) publications respectively. The T- maze and Y-maze assess the ability of mice to identify the most recently explored arm and to enter the novel arm. I identified percentage alternation as the most common unit of assessment which featured in 6 T-maze experiments and all 17 Y-maze experiments (see Figure 3.17).

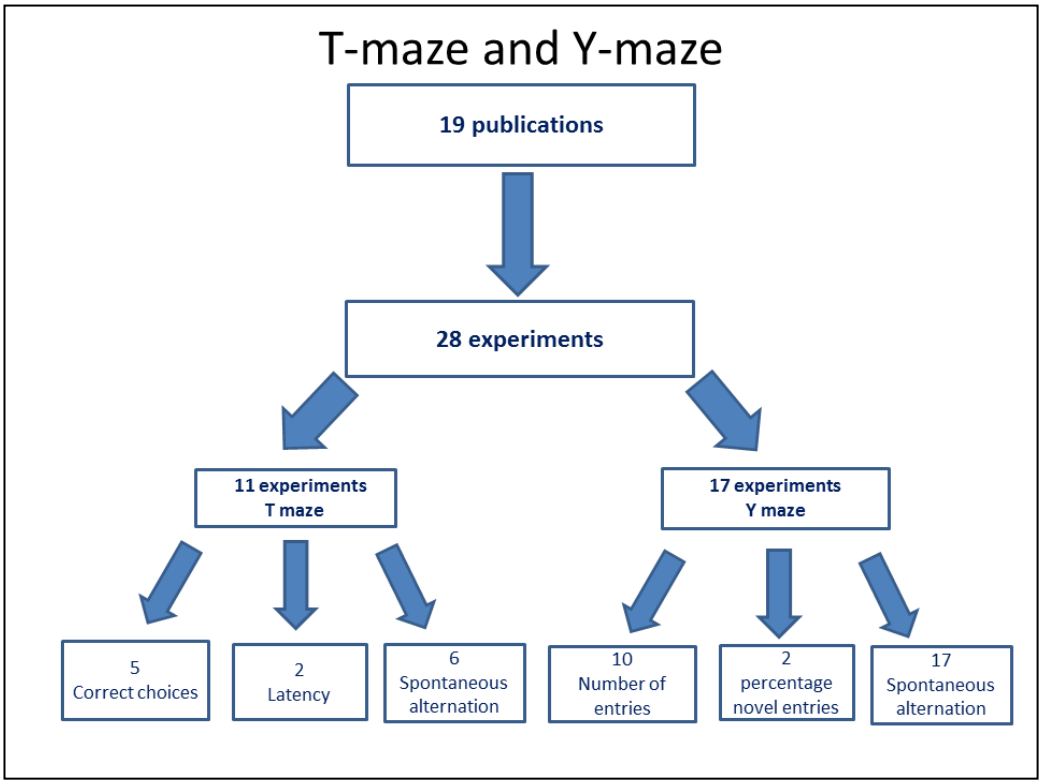


Figure 3.17: 19 publications examined either the T-maze or Y maze and each could be assessed using a variety of methods. T-maze was assessed using 'correct choices', 'latency' or 'spontaneous alternation'. Y-maze was assessed using 'number of entries', 'percentage novel entries' and 'spontaneous alternation'

3.4.5 Novel object recognition tasks

Novel object tasks featured in 15 publications (25 experiments, Figure 3.18). Within this term I included a number of similar studies. The majority of data extracted included the conventional use of the Novel object recognition task where mice were given a familiarisation 'training' period with two blocks, with one of the blocks changed for a novel object (21 experiments). Two experiments were described regarding object placement, whereas one experiment identified performed object context assessment. For units of the outcome measures extracted I applied our prioritisation rule (see methods), taking forward data from 9 experiments regarding time with novel/displaced object and 16 with a measure of recognition index.

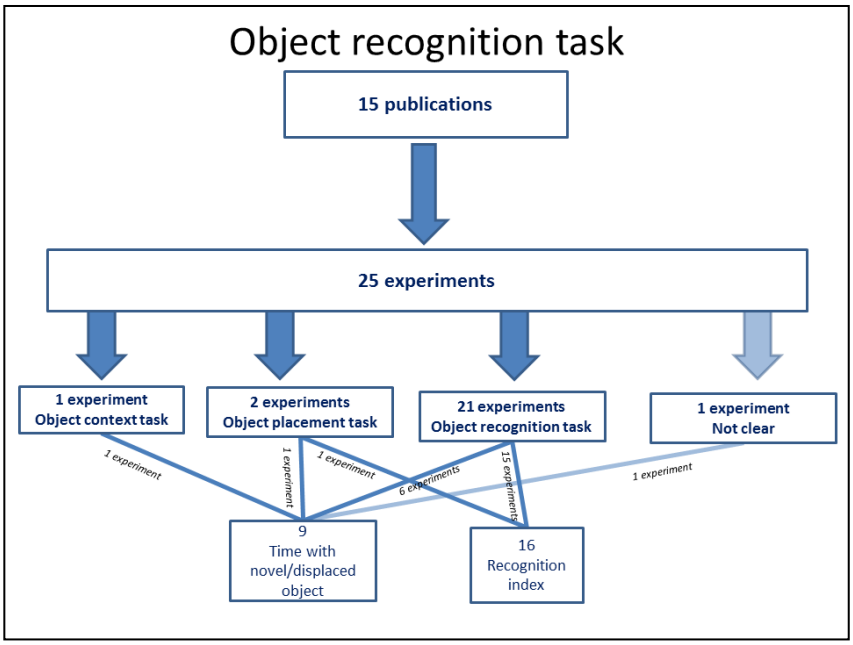


Figure 3.18: 25 publications examined Object recognition tasks and these included a number of variations. Data were extracted for the object context task, object placement task and object recognition task. Where not described, numbers refer to experiments and some experiments examine more than one outcome.

3.4.6 Other neurobehavioural tests

Across all analyses, there are two notable exclusions from the dataset: the open field test and elevated plus maze. For the open field test there were sufficient data to be investigated as an individual paradigm whereas the elevated plus maze (EPM) would be included for a specific publication bias analyses (see Chapter 7). Such paradigms were excluded because transgene effects were not consistent and thus I could not reliably determine the direction of effect (improvement or worsening).

Open field test

I found 15 publications reporting 24 experiments using the open field test of which 18 reported wild type performance. Of these 18 experiments, in seven transgenic mice were less active than controls and in 11 they were more active. I therefore could not be confident in assigning the transgenic direction of effect (Figure 3.19).

Elevated plus maze

Six publications reported eight experiments using the EPM. Similar to the issues outlined with the open field test the dataset suggested inconsistencies regarding the direction of impact of a transgene (Figure 3.20). Where I compared the percentage time in open arms I observed that the presence of a transgene could both increase and decrease time in closed arms. Therefore, I excluded this data from meta-analyses.

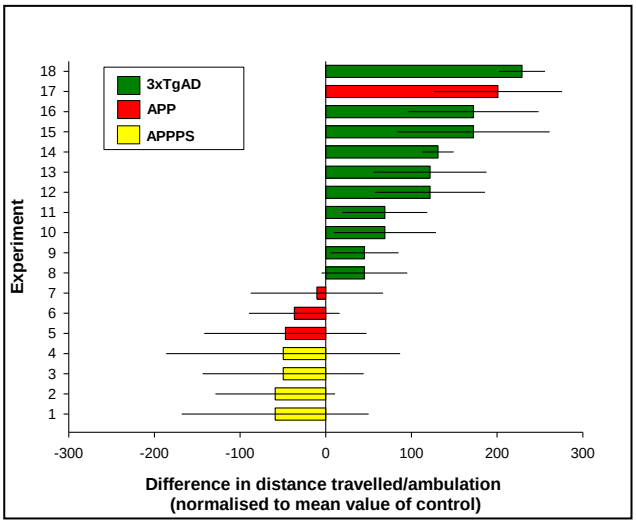


Figure 3.19: For outcomes from the open field test, the presence of a transgene was associated with both an increase and decrease ambulation. Data were 'normalised' whereby control transgenic outcomes equated to 100%. Error represents standard deviation of each estimate and colour represents transgenic model group used.

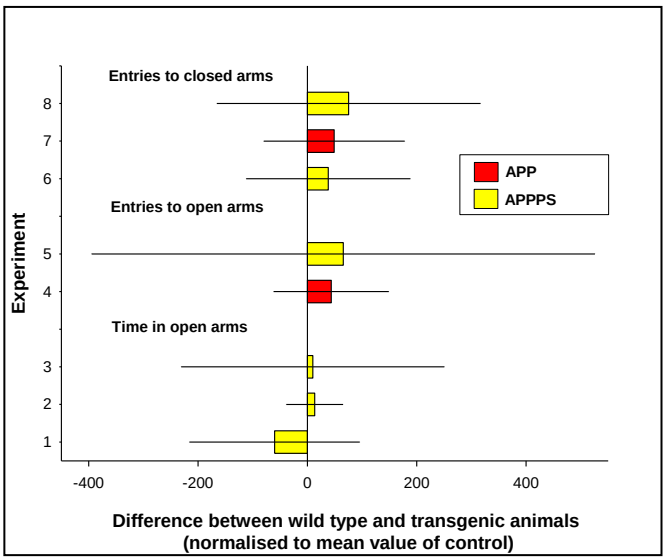


Figure 3.20: For outcomes from the elevated plus maze, the presence of a transgene was associated with both an increase and decrease time in open arms. Data were 'normalised' whereby control transgenic outcomes equated to 100%. Error represents standard deviation of each estimate and colour represents transgenic model group used.

Behavioural paradigm	Description	# pub
Attack latency	Mice are exposed to a particular stressor (e.g. rat) and latency or frequency of attacks is recorded. Transgenic animals are likely to have increased aggression compared to wild type counterparts.	3
Balance beam	Two support columns are connected with a beam above a padded surface. The ability (usually by speed) of the mouse to cross the beam is assessed.	3
Barnes maze	The Barnes maze is a circular, open platform elevated above the floor with a number of dark holes evenly spaced around the perimeter. One of these holes has a hidden platform, and mice are trained to find such a platform using visio-spatial cues (thus similar to the Morris water maze). Transgenic mice commonly have longer latencies or search paths.	5
Cheeseboard maze	Used for the first time in 2008 the cheeseboard maze provides a dry land version of the Morris water maze, where the mouse is trained to find a food reward through a series of training sessions followed by a 'probe' trial or reversal trial.	1
Circular platform task	The circular platform task assesses reference memory to identify a hidden escape hole within a group of many others (i.e. 16 others). Conditions during the experiment may be made aversive for the mice by using a high speed fan and/or high lighting and over a number of days the ability of the mouse to find the 'target' hole is assessed.	2
Closed field symmetrical maze	The closed field symmetrical maze challenges mice to navigate from a startbox to an end box within a walled maze construct. Mice are given a reward for completing the challenge and the complexity of the maze increases at each level.	1
Cued food preference	Mice are exposed to a particular odour, and then exposed to a novel odour. In a similar method to that of the novel object recognition task, the ability of the mice to determine and the new odour is a given measure of memory performance.	1
Elevated Plus Maze	The elevated plus maze is commonly used neurological paradigm used to assess anxiety and consists of four arms in a cross shape, where two arms are enclosed by walls and two open. Time spent in both the open and closed arms can be used representing efficacy. Wild type mice typically spend less time in the open arms than transgenic counterparts.	6
Exploratory Activity	Exploratory activity can be measured through numerous methods infrared beam break counts. The 2 publications examining exploratory activity performed analyses while in cages and thus separates it from open field activity.	2

Fear conditioning	Fear conditioning is a frequently used paradigm in mice which can assess both contextual and cued fear response in a Pavlovian associative learning task. Mice are given training sessions whereby a treatment is given which elicits an innate fear response (e.g. small electric foot shock causing freezing behaviour). Such a fear response is commonly accompanied by a auditory tone or olfactory cue and behavioural assessment may be designed to identically replicate experimental training sessions (contextual assessment) or repeat an associated cue in a novel setting (cued assessment).	**19**
Food preference test	The food preference test is used to assess both olfactory and spatial memory. Briefly, the paradigm involves 'demonstrator' mice which are exposed to transgenic mice after consuming mixed chow with a given aroma. The ability of the transgenic mice to remember the aromatic chow from this exposure is assessed when it is presented alongside plain chow.	**1**
Functional observational battery	A functional observation battery can be used to assess a large number of behavioural outcomes including sensorimotor events, muscle tone, and central nervous system activity and excitability.	**1**
Habituation task	The Habituation task as described in Matsuoka, 2008 provides an olfactory assessment similar to the novel object recognition test in experimental design. Transgenic mice are exposed to a vanilla odour which was changed to almond and the ability of the mouse to distinguish the two was assessed.	**1**
Hole board learning task	Similar in design to the Barnes maze, the hole board learning task was used to assess the ability of a mouse to remember which out of sixteen holes were baited with food. The same holes were consistently baited throughout the use of the paradigm.	**1**
Locomotor activity	Mice were placed in a circular corridor and their innate activity was recorded in term of infrared beam breaks.	**1**
Morris water maze: Acquisition phase	The Morris water maze is the most widely used behavioural paradigm in transgenic mouse models of Alzheimer's disease. Mice are trained to find a hidden platform in a cloudy pool of water thought to be found using extra visual cues. Mice generally take less time to find the platform as the experiment continues, with wild type mice achieve shorter times quicker than transgenic models.	**71**
Morris water maze: Probe phase	Removal of the platform from the pool is required for the probe 'test' phase of the Morris water maze. Mice are assessed for their ability to determine the previous platform location through numerous methods,	**57**
Novel object recognition task	The novel object recognition task assesses the innate tendency that mice will explore a novel, replaced or displaced object whenever presented with one Commonly this paradigm is designed with the mice being exposed to a number of unfamiliar objects for a given period of time (i.e. 5 to 10 minutes). From 30 minutes to 24 hours later, mice are exposed once again to the same environment with one of the objects displaced or replaced and the ability of the mouse to comprehend such a change is quantified by the time spent near the novel or displaced object.	**15**

Open field test	The open field test examines both anxiety and locomotion rodent models by their spontaneous ambulation. Innate behavioural such as grooming or rearing are often used as outcome measures alongside ambulation.	**15**
Passive avoidance	Passive avoidance paradigms commonly involve exposing mice to an electric shock in a specific environment (e.g. a dark compartment of apparatus). The memory of the mouse is assessed by the latency or error to return to environment in which the shock was originally given,	**4**
Platform recognition	The platform recognition task uses the same apparatus as the Morris water maze (circular pool with external cues) and varies the location of a raised visible platform. If Morris water maze has been used previously, this forces mice to change from visio spatial technique to recognition memory	**6**
Radial arm water maze	The Radial arm water maze (RAWM) assesses memory through visio-spatial recognition and can assess both working and reference memory. The paradigm consists of a number of different arms (usually six or 8) centred on a central circular pool of water. There are a number of specific set ups in use including; baiting all or half of the arms of the maze or placing a hidden platform within one arm. Transgenic mice are expected to have slower latencies and increased errors finding goal arms.	**23**
Rotarod	The rotarod is assesses coordination and balance through the use of a spinning rod.	**2**
Spontaneous behaviour	Spontaneous behaviour was measured within cages of mice. Such assessment does not require any specific paradigm apparatus and assesses the presence of stereotypical behaviour.	**1**
String agility	String agility can be used to assess both forepaw grip capacity and agility, typically measured by the time.	**2**
Tail suspension test	Mice are suspended from the tail and videotaped. The ability of the mice to clasp is assessed through a clasping score.	**2**
T-maze	The T maze consists of 3 goal arms (A,B,C) in a T shape. The most commonly assessed parameter is spontaneous alternation- the ability of the mouse to enter an arm which it has not just visited previously. Behaviour in the T maze is thought to reflect the natural tendency mice have to explore novel environments. Transgenic mice typically have lower rates of alternation.	**7**
Traverse beam	Testing balance and general motor co-ordination, the traverse beam tests the ability of mice to reach a goal box through crossing a 51 cm long 1 cm wide wooden beam.	**2**
Y-maze	Almost identical to the T maze, The Y maze consists of 3 goal arms (A,B,C) in a Y shape. Behaviour in the Y maze is thought to reflect the natural tendency mice have to explore novel environments (in this case the unexplored arm). Transgenic mice commonly have lower rates of alternation.	**14**

Table 3.6: Thirty different neurobehavioral paradigms were identified across publications identified. Each is briefly described and the number of publications describing each is given.

3.5 Transgenic mouse model use

Fifty-five individual transgenes were described; each with a unique description of those mutations used to capture aspects of AD. I found the most commonly reported transgenic group was the APP group, reported in 298 publications. More specifically, the Tg2576 mouse was the most commonly reported single transgenic-reported in 34% (149/427) of publications. Eighty-five publications tested both male and female mice. Where a single sex was used, females were more commonly used than males (56 vs. 45 publications). Fifty five percent of publications (236/427) did not state the sex of the animal used. The number of publications describing each specific mutation, alongside transgenic model group and sex can be found in Table 3.8.

The zygosity of transgene expression and promoter used can often be a determining factor a given transgenic phenotype. I identified that 68.9% of publications did not describe the zygosity of the transgenic mouse. For those publications that did, where multiple mutations were present it was not possible to accurately identify whether the described zygosity referred to both or one of the mutations. Within the published literature, 249/427 (58%) publications made specific reference to the promoter used. To improve the statistical power of meta-analyses I decided to cross-check referenced literature wherever possible in order to deduce how transgenes were established. I identified the promoter used for 80% of publications. Four major

promoters were used (Thy-1 gene promoter,], PDGF [Platelet derived growth factor] and HPP [hamster prion promoter]) which were commonly associated with specific strains of transgenic mice. Those promoters identified remained difficult to categorise. For these reasons I took the decision not to take promoter attributes forward for meta-analyses. Table 3.7 provides a simplified summary listing promoters used by transgenic model group.

# promoters	Promoter	3xTgAD	APP	APPPS	Other	PS	Tau	Unknown	Total
Single	HPP		153	3					**156**
	Thy-1	24	50	11		1	2		**88**
	unknown	4	20	42	1	3	5	7	**82**
	PDGF		43			2	2		**47**
	Mouse prion protein promoter		2	21		1	6		**30**
	Syrian HPP		29				1		**30**
	Human cytomegalovirus (CMV)				4				**4**
	Neuron specific enolase						2		**2**
	Forebrain-specific calmodulin kinase II		1				1		**2**
	Thy1 (Human)		2						**2**
	CamKII						1		**1**
	Cytomegalovirus enhancer/b-actin				1				**1**
	Rat specific enolase		1						**1**
	Prion protein gene complex			1					**1**
	hAPP		1						**1**
	Total number of single promoter driven transgenic cohorts								**448**
Multiple	HPP/PDGF			18					**18**
	PDGF/PDGF			2					**2**
	HPP/unknown			1					**1**
	Total number of multiple promoter driven transgenic cohorts								**21**
Grand Total		**28**	**302**	**99**	**6**	**7**	**20**	**7**	**469**

Table 3.7 Simplified summary of use of promoters in transgenic model groups used. Most studies use a single type of promoters to direct transgene expression, but a number used different promoters to promote different mutations.

Transgenic Model Group	Transgene	Both	Female	Male	Unknown	Number of Publications
3xTgAD	3xTgAD	11	3	5	13	**32**
3xTgAD Total		11	3	5	13	**32**
APP	APP	1			3	**4**
	APP23		2	7	6	**15**
	APP51/16			1		**1**
	APP695				1	**1**
	APP695lon/swe				1	**1**
	APP751lon/swe	2	1	1	13	**17**
	APParc (E22G)	1				**1**
	APPlon	3		1	8	**12**
	APPlon/swe	1		1	2	**4**
	APPswe	4	4	2	9	**19**
	APPV717F	4	6	2	16	**28**
	APPV717F (APOE KO)				1	**1**
	APPV717I				1	**1**
	APPV717I-CT100				1	**1**
	APP-YAC				2	**2**
	CamKII ttA x tet APPswe/ind	1				**1**
	J20 APPSWE/IND	2		2	11	**15**
	Tg2576	32	33	16	70	**151**
	TgCRND8	5	5	4	17	**31**
	tgNORBA				1	**1**
	TG-SwDI				2	**2**
APP Total		56	51	37	165	**309**
APPPS	APP23/PS45				1	**1**
	APP24		1			**1**
	APP695K594N,M595L/PS1de9				1	**1**
	APPPS1				3	**3**
	APPswe/PS1	2		1	4	**7**
	APPswe/PS1A246E		1	3	1	**5**
	APPswe/PS1dE9	9	10	11	20	**50**
	APPswe/PS1L166P				2	**2**
	APPswe/PS1M146L	6	1	4	12	**23**
	APPswe/PS1M146V	2	1	1	1	**5**
	APPswe/PS1P246L				1	**1**
	APPswe/PS2N141I				2	**2**
	APPV717F/PS1M146L	1			2	**3**
	APPV717I/PS1A246E	2	1		1	**4**
APPPS Total		22	15	20	51	**108**
Other	AD11	1			3	**4**
	Nse/ps2m				1	**1**
	Tg13592				1	**1**
Other Total		1			5	**6**
PS1	PS1	1				**1**
	PS1dE9		1			**1**
	PS1-L235P		1			**1**
	PS1M146L			1	1	**2**
	PS1M146V	2				**2**
PS1 Total		3	2	1	1	**7**
Tau	GSK-3/VLW				1	**1**
	GSK3betaS9A				1	**1**
	NFT P301S/K257T				1	**1**
	NSE/APPsw				1	**1**
	p25				2	**2**
	P301S/K257T				1	**1**
	pNSE/htau23	1				**1**
	T44				4	**4**
	tau V337M				2	**2**
	tgP301L	3	4	1		**8**
Tau Total		4	4	1	13	**22**
Unknown	unknown				7	**7**
Unknown Total					7	**7**
Grand Total		97	75	64	255	**491**

3.5.1 Age specific parameters

Across all outcomes the median age at intervention administration was 168 days [IQR 84 to 311] and the median age at outcome assessment was 308 days [IQR 175 to 420]. The early age at which interventions are administered in transgenic mouse models has been proposed as a potential explanation for translational failure (Zahs & Ashe 2010). As a representative sample I examined the four most commonly tested transgenic mouse models (Tg2576, TgCRND8, APPswe/PS1de9 and 3xTgAD) in order to inspect the age of intervention administration and outcome assessment by medians and inter-quartile ranges (Figure 3.21). For the Tg2576 and 3xTgAD models, the majority of interventions were given before the onset of plaque pathology but it is interesting to note that intervention administration in the APPswe/PS1de9 transgenic commonly occurs after the onset of plaques. TgCRND8 mice were also interesting in the respect that they offer a relatively quick onset of the phenotype- which may explain why the majority of interventions administered before three months of age. The age disparity identified between transgenics may be of interest for further exploration in meta-analyses.

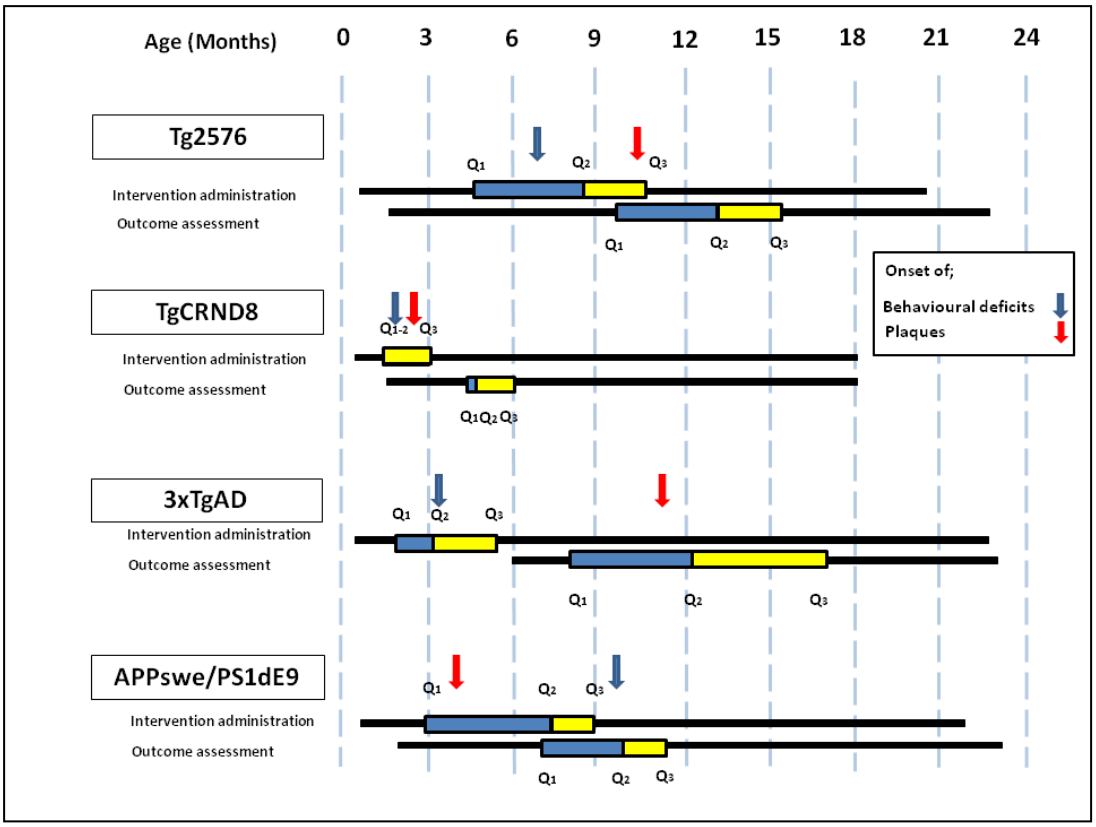


Figure 3.21: The age at which interventions are administered and assessed has been increasing interest in terms of clinical relevance. I examined the four most commonly tested transgenic models (TgCRND8, Tg2576, 3xTgAD, APPswe,/PS1de9) in box and whisper plots for both the age at intervention administration and outcome assessment. Also shown is the onset of behavioural deficits and robust plaque pathology. (Garcia-Alloza et al. 2006;Janus et al. 2000;Sterniczuk et al. 2010;Savonenko et al. 2005)

3.6 Intervention use

357 different interventions were identified within the described literature. I faced significant challenges in classifying most interventions into intervention groups; intervention attributes are not always known and they can have multiple targets. Nonetheless, for illustrative purposes I identified a number of intervention groups including; 'anti-inflammatory interventions' (including gamma secretase inhibitors, 97 publications), 'active immunisation' (99 publications), 'passive immunisation' (102 publications), 'health improvements' (e.g. dietary supplements or exercise, 86 publications), 'beta-secretase Inhibitors', (13 publications) 'pro-inflammatory interventions' (10 publications), 'metals/metal chelators' (26 publications) and 'cholinergic function enhancers' (29 publications). While selected intervention groups and interventions may be subsequently investigated in greater detail, meta-analyses were not planned to compare intervention classifications. For those interventions which report outcomes in 5 or more publications (16 interventions, see Figure 3.22 for further details) I provide further estimates of effect information on these wherever possible (see Chapter 6).

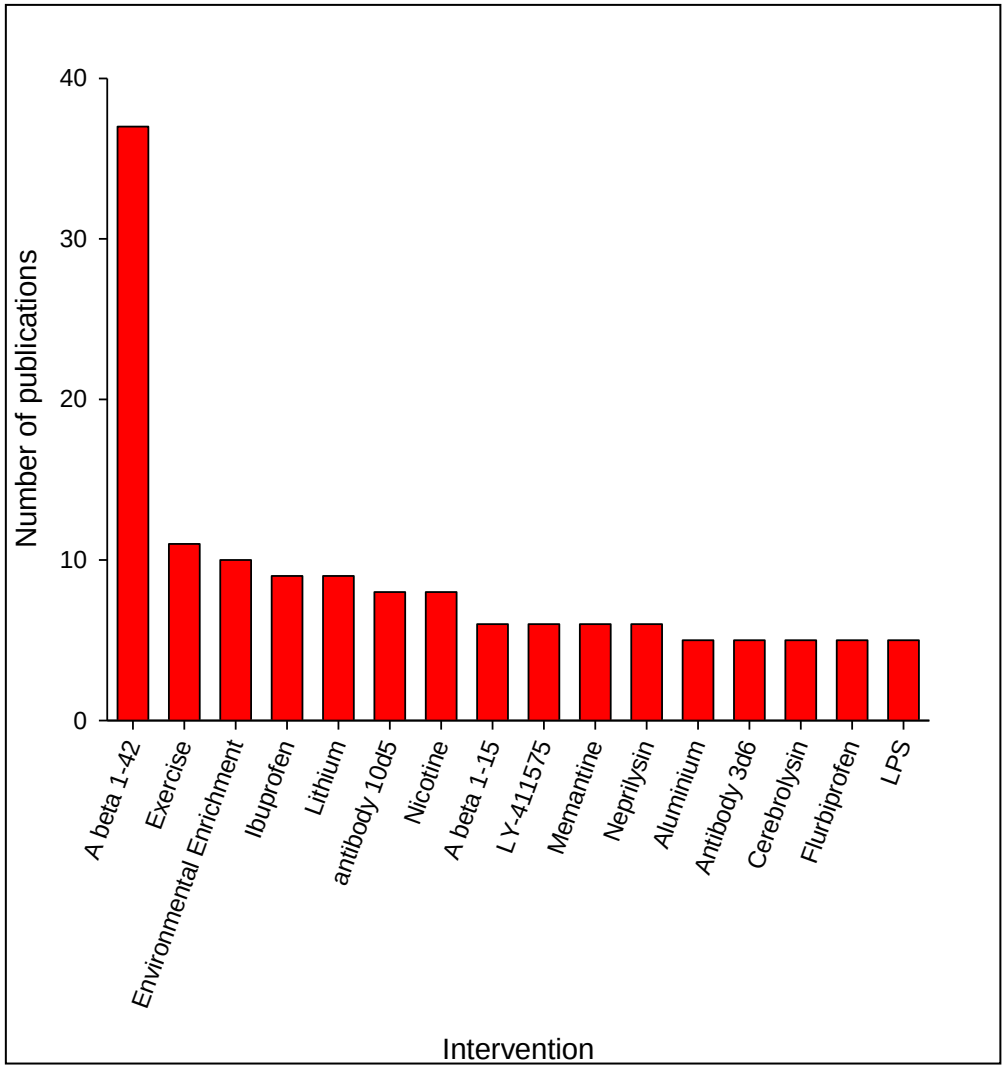


Figure 3.22: The sixteen most commonly tested interventions where outcomes were reported and the number of publications they feature in. Such interventions would be explored using meta-analysis techniques wherever data permitted.

3.6.1 Active immunisation summary

Due to the considerable data, I explored active immunisation experiments in further detail. I noted 24 unique lengths of amyloid beta tested across 77 publications and observed that amyloid beta 1-42 was the most commonly investigated intervention (41 publications).

In terms of the mode of administration, amyloid beta was most frequently administered as a peptide (19 publications) and it was also administered pre-transcription genetic coding in seven publications. The diversity of how amyloid was packaged for active immunisation was considerable. There were 62 uniquely described adjuvants or vectors (such as Freund's adjuvant or the Adeno-viral vector [AVV]). A summary of the diverse nature of amyloid beta active immunisation can be found in Figure 3.23.

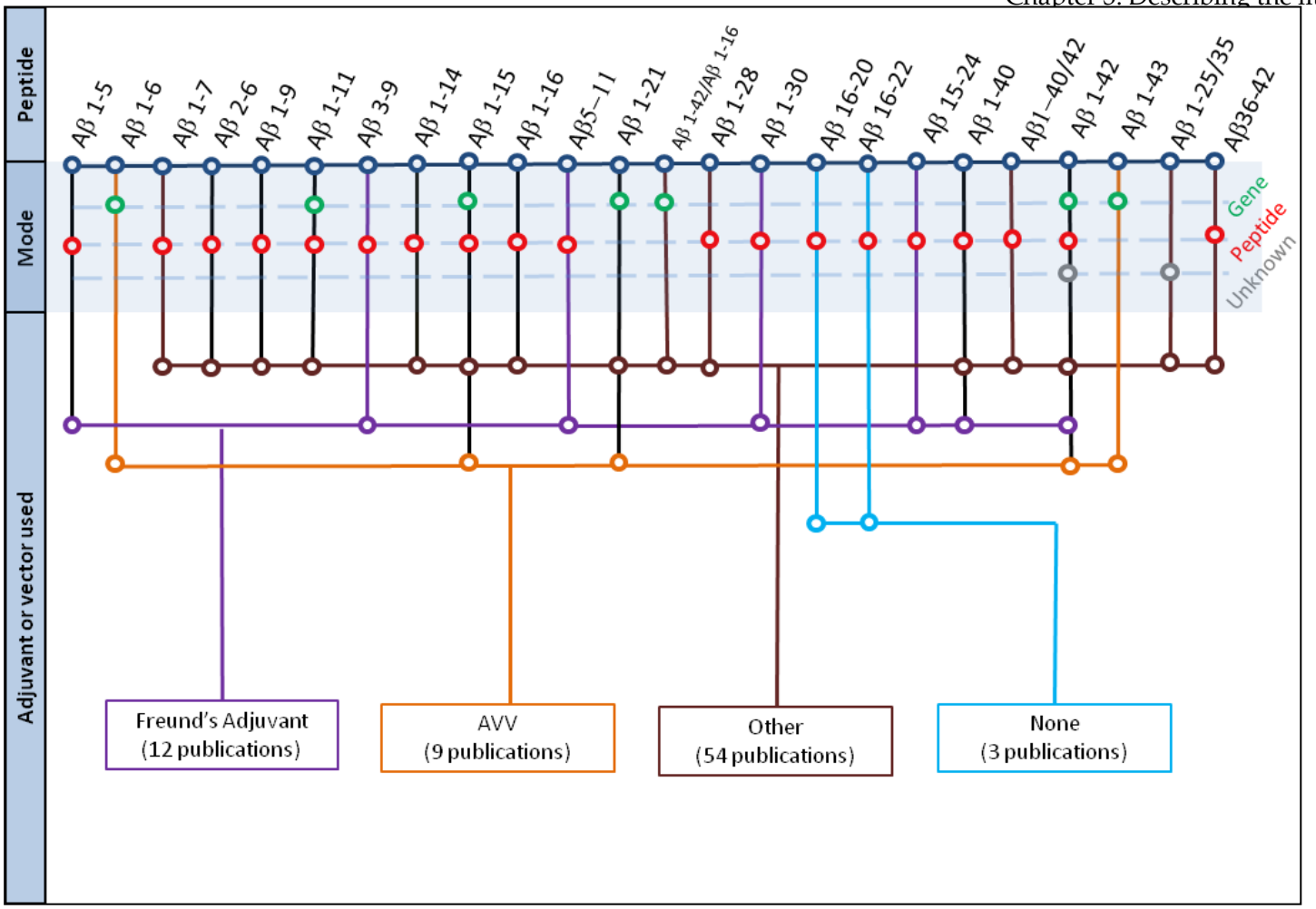


Figure 3.23: The administration of amyloid beta as an active immunisation strategy is truly diverse: through the fragment of amyloid administered, the mode of administration (genetic or peptide) and whether an adjuvant or peptide has a role in administration. AVV: Adeno-virus Vector, Aβ Amyloid beta.

3.7 Study quality

3.7.1 Study quality items

Reported study quality score was assessed across the 427 publications. Random allocation to group was reported by 67 of 427 publications (16%), blinded assessment of outcome by 94/427 (22%), a statement of potential conflict of interest by 54/427 (13%), compliance with animal welfare regulations by 239/427 (56%); and no publication described how the group size of the experiment was determined. I examined how study quality changed over time where the only criterion which demonstrated consistent improvement was reporting of compliance with animal welfare legislation (Figure 3.24). See Chapter 7 for meta-analyses of study quality items.

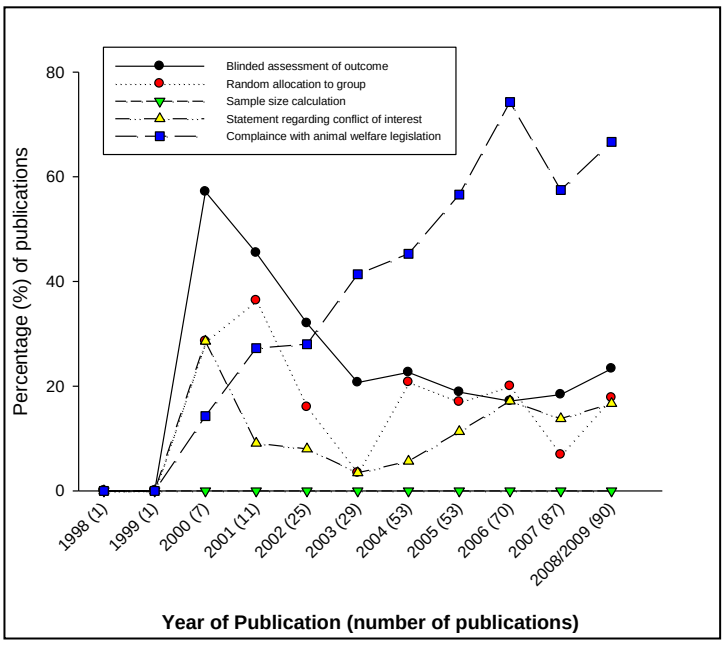


Figure 3.24: Percentage of publications meeting each of the five study quality criteria. Total number of publications per year is described in brackets.

3.7.2 Outcomes reported

The use of the study quality item list was a pre-specified attempt to assess study quality. There were also other notable study quality markers from working with the published literature; four percent of authors (16/427) were contacted due to inadequate description of fundamental study methodology such as the number of animals used or the age at intervention administration. Furthermore, for every 15 articles read, one would fail to state whether error bars represented standard error or standard deviation and emailing authors aided subsequent interpretations (7% of literature).

3.8 Overview of existing literature

Our systematic review has identified a dataset with extensive methodological variation, particularly with respect to the transgenic models used, interventions tested, the age at intervention administration and outcome assessment.

Seven major outcome measures were reported from publications (plaque burden, amyloid beta 40, amyloid beta 42, tau, cellular infiltrates, neurodegeneration and neurobehaviour) and I will summarise overall estimates of efficacy wherever possible. Further, wherever data permit I will investigate relationships within and between outcomes.

Over the next three chapters I describe such analyses: in Chapter 4 I examine individual outcome measures and relationships between outcome measures; in Chapter 5 I examine relationships between observed efficacy and age and sex, alongside inspecting the impact of the transgene within models. In Chapter 6 I provide summary analyses inspecting individual interventions.

Chapter 4: Outcome measure specific meta-analyses

In this chapter I perform meta-analyses on each of the main pathological and neurobehavioural outcomes extracted. To quantify the impact across all interventions on a given outcome, I derive overall summary estimates of efficacy. To ensure I account for fundamental differences between models I also stratify outcome estimates by the transgenic group used. I then explore methodologies within each outcome and where data are sufficient I investigate relationships within a given outcome measure. To address limitations in our understanding of how different outcome measures relate to one another I investigate relationships between outcomes wherever data permit. Throughout, analyses conducted are not designed specifically around a specific disease hypothesis; they are conducted to reflect characteristics of the dataset identified.

Pathological outcomes

For pathological outcomes I initially planned to use normalised meta-analysis estimates of effect size (see Methods). However, only 9% of publications described wild type data and because some AD like pathology was present in such estimates, this ruled out the use of the technique. Methodologies were too diverse to allow difference in means estimates and thus I decided to use standardised mean difference meta-analysis.

4.1 Plaque burden

I identified 414 experiments (representing 5157 animals) which reported changes in plaque burden and overall interventions reduced plaque pathology by 0.98 SD (95% CI 0.87 to 1.08). Ipartitioned heterogeneity in order to assess whether there was an association between the staining technique used and reported outcome but this did not account for a significant proportion of the observed heterogeneity (χ^2=0.5). I identified that publications most commonly referred to immunohistochemical staining methods (91%, [378/414]) where the overall reduction in plaque pathology was estimated at 0.98 SD (0.87 to 1.10). Thirty-nine experiments used congo red staining which had an estimated reduction of 0.98 SD (0.56 to 1.41). For the 65 experiments which used Thioflavin S Iestimated a 0.91 SD (0.67 to 1.14) reduction in plaque pathology.

	Immunohist. staining	Congo red staining	Thioflavin S staining	Summary estimate*
Effect size	0.98 SD	0.98 SD	0.91 SD	0.97
95% CI	(0.87 to 1.10)	(0.56 to 1.41)	(0.67 to 1.14)	(0.87 to 1.07)
n	**378**	**39**	**65**	**482**

Table 4.1: Estimates of standardised effect size according to each staining method used. Columns represent different staining techniques (immunohistochemistry [immunohist], congo red, Thioflavin S) and end column indicates summary estimates , *as different outcomes can be represented in the same cohort of animals some are represented more than once. Brackets provide 95 percent confidence limits and lower number indicates the number of experiments (n).

I identified that sufficient data were present to explore relationships further: between antibody stained plaques, congo red (32 experiments) and Thioflavin S (36 experiments, Table 4.2).

Staining method	Antibody Effect size 95% CI and n	Congo red Effect size 95% CI and n	Thioflavin S Effect size 95% CI and n	Combined Effect size 95% CI and n
Antibody stained only	0.95 SD (0.83 to 1.08) **310**			0.95 SD (0.83 to 1.08) **310**
Congo stained only		0.57 SD (-0.01 to 1.15) **7**		0.57 SD (-0.01 to 1.15) **7**
Thioflavin S stained only			1.13 SD (0.82 to 1.43) **29**	1.13 SD (0.82 to 1.43) **29**
Antibody and Congo red stained	1.27 SD (0.76 to 1.78) **32**	1.09 SD (0.58 to 1.60) **32**		1.17 SD (0.68 to 1.65) **32**
Antibody and Thioflavin S stained	0.94 SD (0.57 to 1.32) **36**		0.73 SD (0.40 to 1.06) **36**	0.84 SD (0.51 to 1.17) **36**
Congo red and Thioflavin S stained		No data	No data	No data
Antibody. Congo red and Thioflavin S stained	No data	No data	No data	No data
	Summary estimate	**Summary estimate**	**Summary estimate**	**Global estimate**
	0.98 SD (0.87 to 1.10) **378**	0.98 SD (0.56 to 1.41) **39**	0.91 SD (0.67 to 1.14) **65**	0.98 SD (0.87 to 1.08) **414**

Table 4.2: Estimates of standardised effect size according to each combination of staining method used for plaque burden. Columns represent different staining techniques (immunohistochemistry, congo red, Thioflavin S) and end column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments.

4.1.1 Plaque burden outcomes and transgenic model group

In order to understand transgene effects on observed effect size I stratified plaque burden data according to the transgenic group used. I assessed heterogeneity for data overall and for antibody stained plaques due the high prevalence of reported experiments (representing 91% of cohorts). Where I stratified plaque burden data overall I identified that estimates were generally similar and this accounted for a significant proportion of the observed heterogeneity (χ^2=12.04, df=4, p<0.05). Where I stratified antibody stained plaque burden data only according to the transgenic model group used I also found that this did account for a significant proportion of the observed heterogeneity (χ^2=18.04, df=3, p<0.01) (See Table 4.3 and Figure 4.1).

Transgenic model Group	Antibody Effect size 95% CI and n	Congo red Effect size 95% CI and n	Thioflavin S Effect size 95% CI and n	Combined Effect size 95% CI and n
APP	0.99 (0.86 to 1.12) **268**	0.79 (0.18 to 1.41) **18**	0.94 (0.63 to 1.24) **48**	0.99 (0.86 to 1.11) **295**
APPPS	0.91 (0.65 to 1.17) **79**	1.11 (0.54 to 1.68) **21**	0.86 (0.42 to 1.3) **13**	0.89 (0.65 to 1.14) **85**
3xTgAD	1.11 (0.46 to 1.75) **24**	No data	0.95 (-0.03 to 1.94) **3**	1.05 (0.46 to 1.64) **26**
Tau	No data	No data	0.41 (-0.53 to 1.35) **1**	0.41 (-0.53 to 1.35) **1**
Other	1.77 (1.05 to 2.49) **7**	No data	No data	1.77 (1.05 to 2.49) **7**
	Summary estimate	**Summary estimate**	**Summary estimate**	**Global estimate**
	0.98 SD (0.87 to 1.10) **378**	0.98 SD (0.56 to 1.41) **39**	0.91 SD (0.67 to 1.14) **65**	0.98 SD (0.87 to 1.08) **414**

Table 4.3 (Previous page): Estimates of standardised effect size for plaque burden staining methods according to each transgenic model group used. Columns represent different staining techniques (immunohistochemistry, congo red, Thioflavin S) and end column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. (N.B. some experiments are represented more than once).

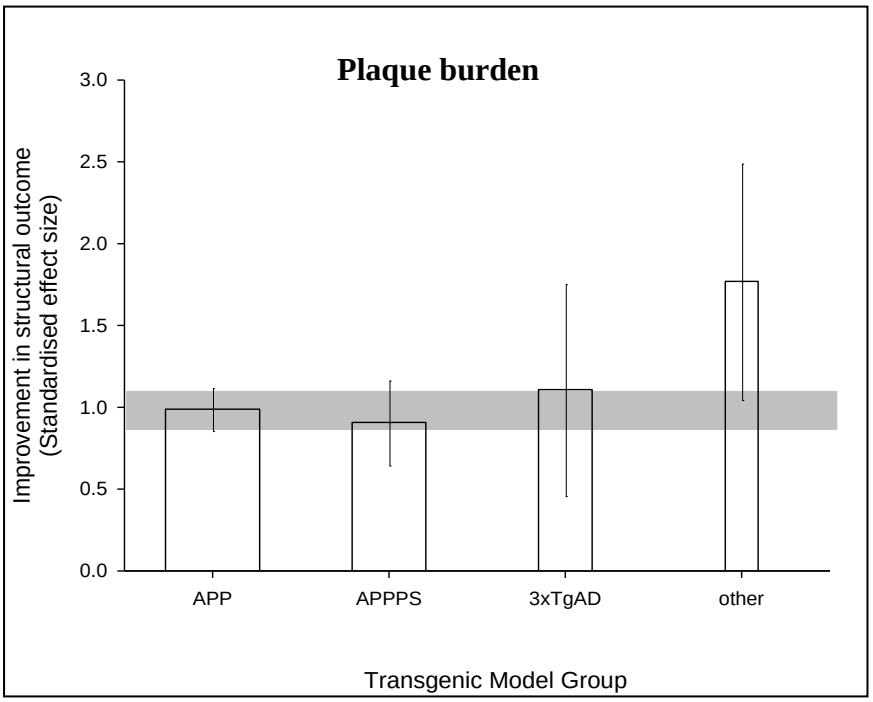
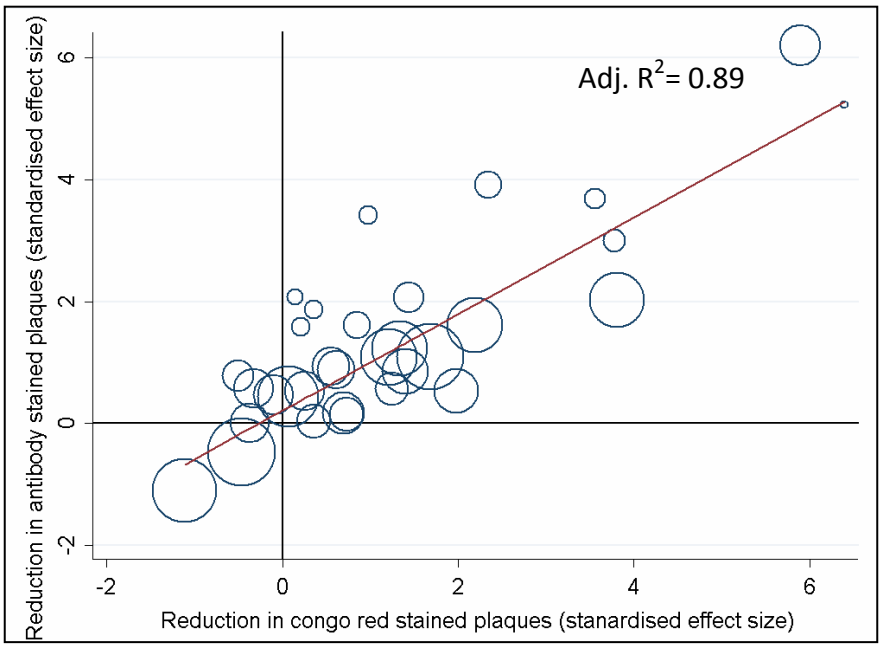


Figure 4.1: I stratified plaque burden data according to transgenic model group used. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

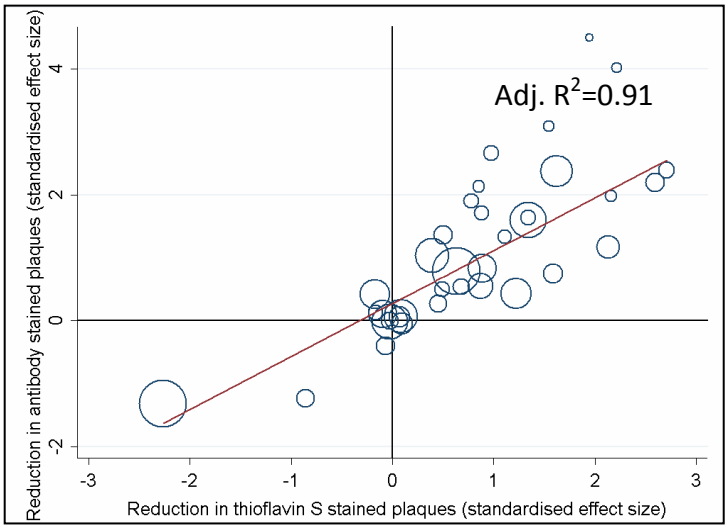
4.1.2 Relationships within different plaque staining techniques

Wherever sufficient data were present (>10 experiments) I performed meta-regression in order to identify potential relationships between the different staining techniques of plaque burden. For 32 experiments I identified that changes in plaque burden stained by congo red could explain 89% of the changes in antibody stained plaques (Figure 4.2). Likewise, 36 experiments suggested that changes in plaque burden stained by Thioflavin S stained plaques could explain 91.1% changes in immunohistochemically stained plaques (Figure 4.3).



Co-efficient (Effect size)	Standard Error	τ	P>|t| where α=0.03	Lower 95% CI	Upper 95% CI	N	Adj. R^2
0.792	0.088	8.99	0	0.612	0.972	32	0.89

Figure 4.2 (upper) and Table 4.4 (lower): 88.7% of changes of immunohistochemically stained plaques could be explained by changes in congo red stained plaques. Each symbol represents an individual experiment and symbol size represents the inverse variance for each estimate of effect size. For each comparison table provides co-efficient, standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and adjusted R^2 (Adj. R^2)



Co-efficient (SMD Effect size)	Standard Error	τ	P>|t| where α=0.03	Lower 95% CI	Upper 95% CI	N	Adj. R^2
0.839	0.094	8.92	0	0.648	1.03	36	0.91

Figure 4.3 (upper) Table 4.5 (lower): 91.1% of changes in immunohistochemically stained plaques could be explained by changes in thioflavin S. Each symbol represents an individual experiment and symbol size represents the inverse variance for each estimate of effect size. For each comparison table provides co-efficient, standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and adjusted R^2 (Adj. R^2)

4.1.3 Plaque burden summary

In summary, estimates of efficacy did not differ according to the staining technique used and but I identified differences between transgenic groups where stratifying immunohistochemically stained plaque burden. Immunohistochemistry techniques were the most commonly assessed and were associated with smaller variances on estimates of efficacy. For these reasons I decided to limit subsequent analyses to immunohistochemically stained plaques only.

4.2 Amyloid beta species

I identified 483 experimental cohorts which examined amyloid species (amyloid beta 40, amyloid beta 42, total amyloid beta or oligomer species) representing 6525 animals. From 483 experiments the overall estimated reduction in amyloid was 0.79 SD (0.70 to 0.87).

I partitioned heterogeneity in order to assess whether the amyloid species assessed impacted on observed outcome but this did not account for a significant proportion (χ^2=11.21, df=3, Table 4.6). Interventions reduced amyloid beta 40 by 0.68 SD (0.57 to 0.79), amyloid beta 42 by 0.78 (0.67 to 0.88), total amyloid beta by 0.83 SD (0.62 to 1.05) and oligomer species by 0.79 SD (0.42 to 1.17).

	Amyloid beta 40	Amyloid beta 42	Total amyloid	Oligomer species	Summary
Effect size	0.68	0.78 SD	0.83	0.79	0.74
95% CI	(0.57 to 0.79)	(0.67 to 0.88)	(0.62 to 1.05)	(0.42 to 1.17)	(0.67 to 0.81)
n	**388**	**389**	**81**	**33**	**891**

Table 4.6: Estimates of standardised effect size according to each species of amyloid assessed. End column indicates combined estimates, *as different outcomes can be represented in the same cohort of animals some are represented more than once. Brackets give 95 percent confidence limits and lower number indicates the number of experiments.

I explored this dataset further and identified that there were sufficient data to investigate number of potential relationships between different amyloid species as shown in Table 4.7.

	Amyloid beta 40 Effect size 95% CI and n	Amyloid beta 42 Effect size 95% CI and n	Total amyloid Effect size 95% CI and n	Oligomer spec Effect size 95% CI and n	Combined Effect size 95% CI and n
Amyloid beta 40 only	1.42 (0.92 to 1.91) **54**				1.42 SD (0.92 to 1.91) **54**
Amyloid beta 42 only		0.56 (0.3 to 0.83) **34**			0.56 (0.3 to 0.83) **34**
Total amyloid only			0.94 (0.59 to 1.29) **31**		0.83 (0.62 to 1.05) **79**
Oligomer species only				0.60 (0.04 to 1.16) **8**	0.60 (0.04 to 1.16) **8**
Amyloid beta 40 and amyloid beta 42	0.62 (0.51 to 0.73) **334***	0.74 (0.63 to 0.85) **334***			0.72 SD (0.62 to 0.82) **334**
Amyloid beta 40 and total amyloid	0.47 (0.12 to 0.82) **28***		0.51 (0.14 to 0.88) **28***		0.53 (0.2 to 0.85) **28***
Amyloid beta 40 and oligomers	0.61 (0.22 to 1) **24***			0.83 (0.36 to 1.31) **24***	0.68 (0.31 to 1.04) **24***
Amyloid beta 42 and total amyloid		1.15 (0.79 to 1.52) **49**	0.78 (0.49 to 1.06) **49**		0.92 (0.64 to 1.19) **49**
Amyloid beta 42 and oligomers		0.74 (0.34 to 1.13) **24***		0.83 (0.36 to 1.31) **24***	0.73 (0.38 to 1.09) **24***
Total amyloid and oligomers			1.69 (-0.2 to 3.58) **3**	2.50 (0.46 to 4.54) **3**	2.17 (0.35 to 3.99) **3**
	Summary estimate	**Summary estimate**	**Summary estimate**	**Summary estimate**	**Global estimate**
	0.68 (0.57 to 0.79) **388**	0.78 SD (0.67 to 0.88) **389**	0.83 (0.62 to 1.05) **81**	0.79 (0.42 to 1.17) **33**	0.78 SD (0.69 to 0.87) **483**

Table 4.7: Estimates of standardised effect size according to each amyloid species assessed. Columns represent different species including amyloid beta 40, amyloid beta 42, total amyloid and oligomer species. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. >10 experiments were sufficient for meta-regreesion*.

4.2.1 Amyloid beta outcomes stratified transgenic model group

As 93% of experiments were represented by either amyloid beta 40 or amyloid beta 42 I decided to focus analyses on these two species individually (Table 4.8). I additionally provide estimates of efficacy for total amyloid and all amyloid species with the exception of oligomers due to limited data.

Overall, I identified that stratifying all amyloid data according to the transgenic model used accounted for a significant proportion of the observed heterogeneity (χ^2 = 38.4, $p<0.05$, Table 4.8). Where I analysed changes in amyloid beta 40 outcomes according to transgenic model group this accounted for a significant proportion of the observed heterogeneity (χ^2 = 25.34, $p<0.01$): higher estimates of effect size were associated with the tau transgenic group, 3.06 SD (1.68 to 4.43) compared to the 'other transgenic model groups assessed (Figure 4.4). For amyloid beta 42 outcomes, stratifying data by transgenic model group used also accounted for a significant proportion of the observed heterogeneity (χ^2 = 22.42, $p<0.01$) where higher estimates of efficacy were found in the Tau, PS and the other transgenic group compared to APP, APPPS or 3xTgAD groups (Figure 4.5).

Transgenic model Group	Amyloid beta 40 Effect size (95% CI) and N	Amyloid beta 42 Effect size (95% CI) and N	Total amyloid beta Effect size (95% CI) and N	Combined Effect size (95% CI) and N
APP	0.76 (0.63 to 0.89) **292**	0.88 (0.75 to 1) **288**	0.84 (0.63 to 1.05) **71**	0.86 (0.76 to 0.97) **368**
APPPS	0.55 (0.31 to 0.8) **61**	0.61 (0.37 to 0.84) **67**	0.79 (-1.19 to 2.76) **8**	0.62 (0.39 to 0.85) **70**
3xTgAD	0.32 (0.05 to 0.6) **33**	0.31 (0.03 to 0.59) **31**	0.43 (0.02 to 0.83) **2**	0.35 (0.1 to 0.59) **33**
Tau	3.06 (1.68 to 4.43) **1**	1.9 (0.27 to 3.54) **1**	**No data**	2.57 (1.45 to 3.69) **2**
PS1	-0.27 (-1.52 to 0.98) **1**	2.13 (0.4 to 3.85) **1**	**No data**	0.55 (-0.46 to 1.56) **1**
Other	**No data**	2.23 (0.33 to 4.12) **1**	**No data**	2.23 (0.33 to 4.12) **1**
	Summary estimate	**Summary estimate**	**Summary estimate**	**Global estimate**
	0.68 (0.57 to 0.79) **388**	0.78 (0.67 to 0.88) **389**	0.83 (0.62 to 1.05) **81**	0.79 (0.7 to 0.88) **475**

Table 4.8: Changes in amyloid species stratified according to the transgenic model group used. Columns represent different standardised effect sizes of amyloid species (amyloid beta 40, amyloid beta 42, total amyloid beta) and end column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. As different outcomes can be represented in the same cohort of animals some are represented more than once.

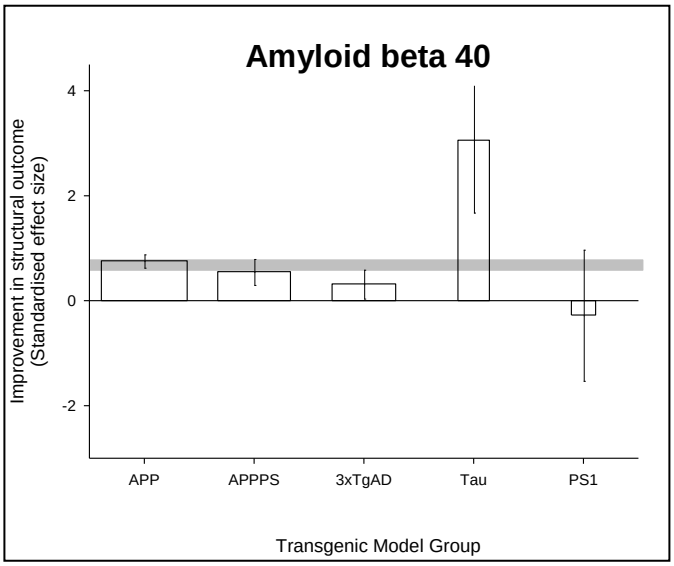


Figure 4.4: I stratified amyloid beta 40 data according to transgenic model group used which accounted for a significant proportion of heterogeneity. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

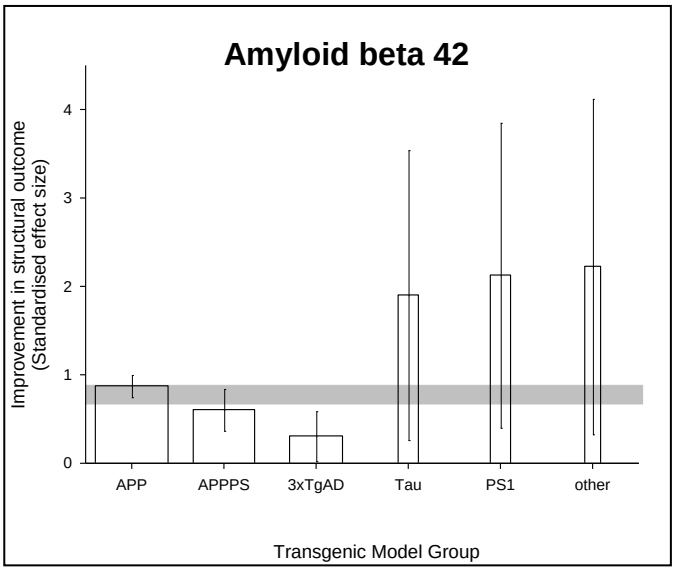


Figure 4.5: I stratified amyloid beta 42 data according to transgenic model group used which accounted for a significant proportion of heterogeneity. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.2.2 Relationships between different amyloid fragments

Where sufficient data permitted, I examined different amyloid species for potential relationships (see Table 4.9 for overview). 334 experiments reported changes in amyloid beta 40 and amyloid beta 42 and meta-regression suggested that changes in amyloid beta 42 could explain 88.4% of changes in amyloid beta 40) $p<0.01$, Figure 4.6).

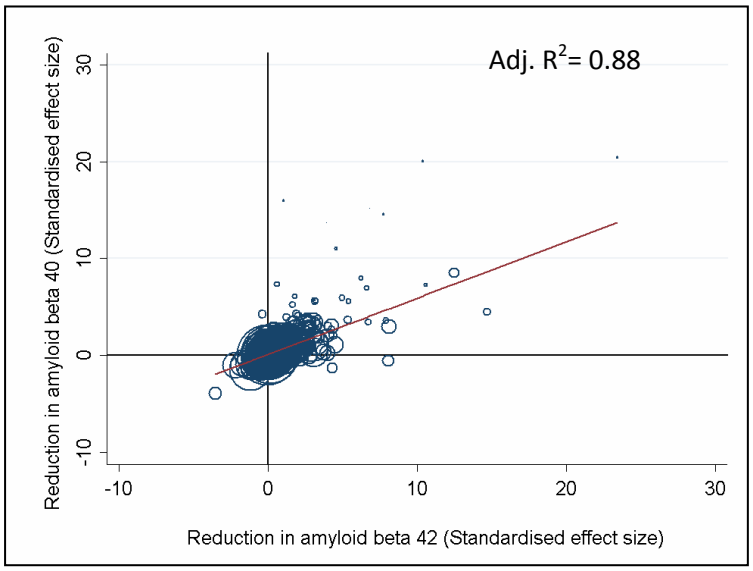


Figure 4.6: 88.4% of changes in amyloid beta 40 could be explained by the observed changes in amyloid beta 42. Cohorts where both were measured are represented with symbol size representing the inverse of the variance for each estimate of effect size.

For the 28 experiments which examined both amyloid beta 40 and total amyloid beta meta-regression identified strong correlation between variables, where changes in amyloid beta 40 could explain 73.7% of changes in total amyloid beta ($p<0.01$, Figure 4.7).

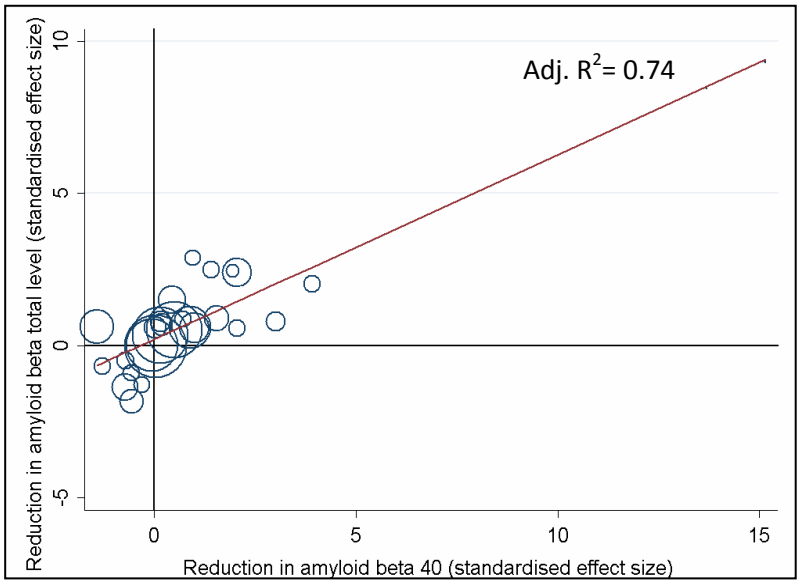


Figure 4.7: 73.7% of changes in total amyloid beta could be explained by the observed changes in amyloid beta 40. Cohorts where both were measured are represented with symbol size representing the inverse of the variance for each estimate of effect size.

For the 24 experiments which reported changes in amyloid beta 40 alongside oligomer species meta-regression suggested 34% correlation (Figure 4.8) but this did not prove statistically significant. For the 49 experiments which examined both amyloid beta and total amyloid levels, meta-regression identified that 50.3% of the variation in total amyloid could be explained by the variation observed in amyloid beta 42 ($p<0.01$, Figure 4.9)

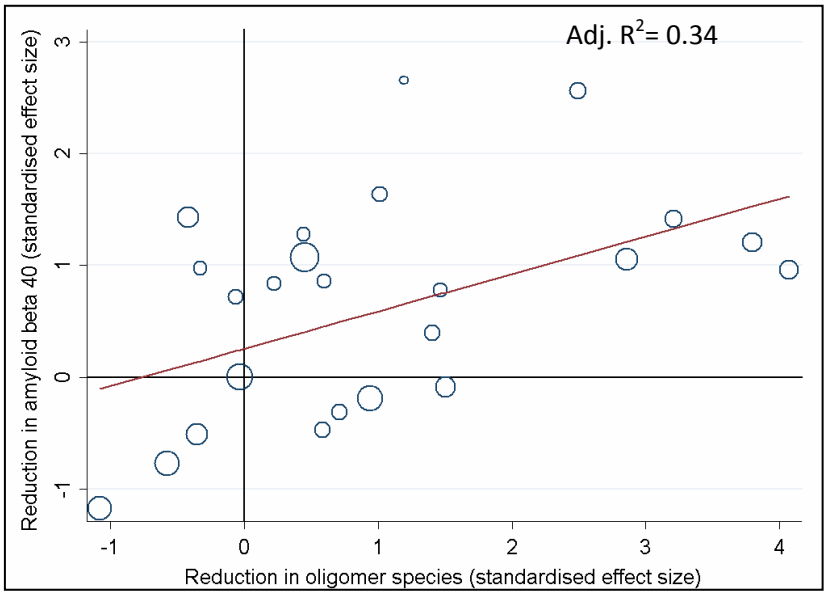


Figure 4.8: 34.0% of changes in amyloid beta 40 could be explained by the observed changes in oligomers. Cohorts where both were measured are represented with symbol size representing the inverse of the variance for each estimate of effect size.

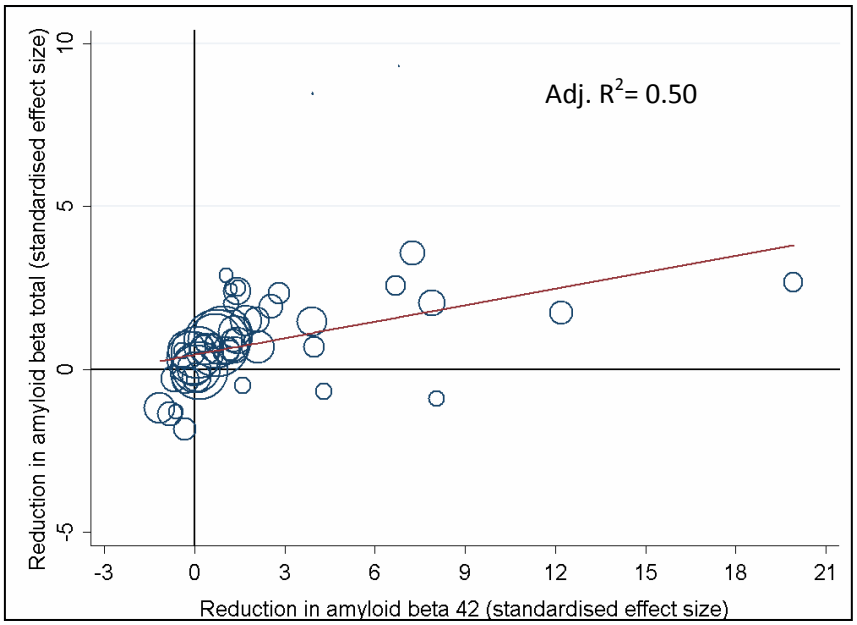


Figure 4.9: 50.3% of changes in total amyloid could be explained by the observed changes in amyloid beta 42. Cohorts where both were measured are represented with symbol size representing the inverse of the variance for each estimate of

Twenty four experiments reported changes in amyloid beta 42 and oligomer species. Meta-regression identified that changes in oligomers could explain 25.7 % of changes in amyloid beta 42 although this did not prove statistically significant for our bonferroni corrected (5 comparisons, α= 0.01, Figure 4.10, Table 4.9).

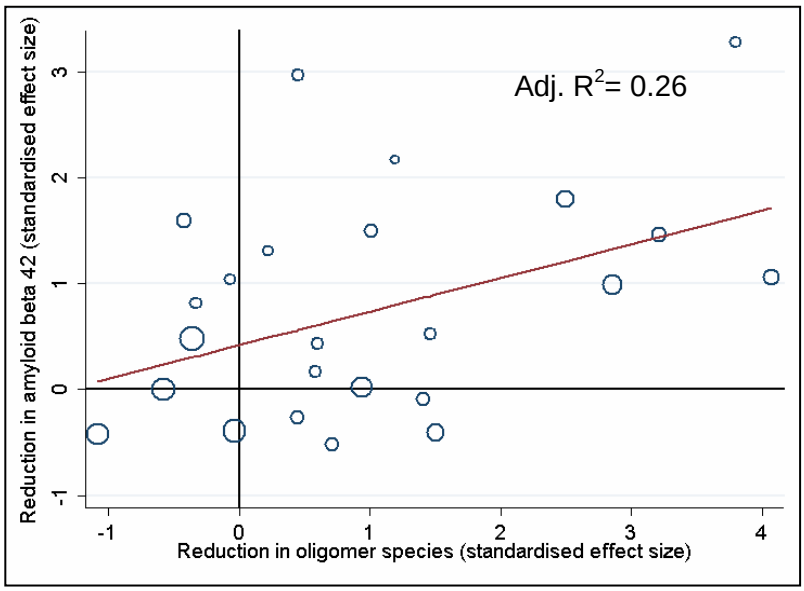


Figure 4.10: 25.7% of changes in oligomers could be explained by the observed changes in amyloid beta 42. Cohorts where both were measured are represented with symbol size representing the inverse of the variance for each estimate of effect size.

	Co-efficient (SMD ES)	Standard error	τ	P>|t| **where α=0.01**	Lower 95% CI	Upper 95 CI%	N	Adj. R^2
Amyloid beta 40 vs. 42	0.580	0.032	18.09	0	0.517	0.643	334	0.88
Oligomers vs. amyloid beta 40	0.335	0.122	2.74	0.012	0.082	0.589	24	0.34
Amyloid beta 40 vs. total	0.607	0.135	4.5	0	0.33	0.884	28	0.74
Amyloid beta 42 vs. total	0.169	0.041	4.14	0	0.087	0.252	49	0.5
Oligomers vs. amyloid beta 42	0.317	0.138	2.29	0.032	0.03	0.604	24	0.26

Table 4.9: Wherever there were sufficient data I investigated potential relationships between amyloid species. For each comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

4.2.3 Solubility of amyloid species

Within amyloid species I explored the data to identify the number of experiments and estimates of effect across the different solubilities of amyloid (Table 4.10). This was possible for 71% (276/388) amyloid beta 40 experiments which revised the overall effect size to 0.66 SD (0.54 to 0.78). 76% (295/389) of amyloid beta 42 experiments stated solubility which revised the overall effect size to 0.76 SD (0.64 to 0.88). For total amyloid 77% (62/81) experiments stated solubility which revised the overall effect size to 0.75 (0.52 to 0.99). For oligomer species, 48% (16/33) of experiments described soluble experiments where the estimated effect size was 1.68 SD (1.09 to 2.27).

	Soluble	Insoluble	Total	Combined
	Effect size (95% CI) and N	Effect size (95% CI) and N	Effect size (95% CI) and N	Effect size (95% CI) and N
Amyloid beta 40	0.58 (0.42 to 0.73) **196**	0.63 (0.48 to 0.79) **166**	0.79 (0.49 to 1.08) **66**	0.66 (0.54 to 0.78) **276**
Amyloid beta 42	0.56 (0.4 to 0.72) **187**	0.63 (0.47 to 0.79) **162**	0.55 (0.26 to 0.83) **52**	0.76 (0.64 to 0.88) **295**
Amyloid beta total	1.01 (0.43 to 1.59) **20**	1.01 (0.43 to 1.59) **20**	0.79 (0.5 to 1.09) **44**	0.75 (0.52 to 0.99) **62**
Oligomers	1.65 (1.09 to 2.21) **16**	No data	No data	1.65 (1.09 to 2.21) **16**
	Summary estimate	Summary estimate	Summary estimate	Global estimate
	0.70 (0.57 to 0.84) **233**	0.73 (0.59 to 0.86) **209**	0.89 (0.69 to 1.09) **110**	0.77 (0.67 to 0.87) **348**

Table 4.10: Summary of the solubility of amyloid species examined. For each outcome (amyloid beta 40, amyloid beta 42 total amyloid beta and oligomer species) soluble, insoluble, total and combined estimates of standardised effects sizes are given. The combined effect size for each species where solubility is stated the end column whereas overall solubility is shown in the end row.

I therefore explored amyloid beta 40 outcomes to identify the spread of data. Sufficient data were present to examine the relationship between soluble and insoluble species (144 experiments) however there were insufficient data to examine any other solubility relationships (Table 4.11).

	Soluble	Insoluble	overall	Combined
	Effect size (95% CI) and N	Effect size (95% CI) and N	Effect size (95% CI) and N	Effect size (95% CI) and N
Soluble only	0.63 (0.27 to 0.99) **45**			0.63 (0.27 to 0.99) **45**
Insoluble only		1.01 (0.57 to 1.46) **22**		1.01 (0.57 to 1.46) **22**
Overall			0.78 (0.44 to 1.11) **58**	0.78 (0.44 to 1.11) **58**
Soluble and insoluble	0.56 (0.38 to 0.73) **144**	0.57 (0.41 to 0.74) **144**		0.59 (0.45 to 0.74) **144**
Soluble and overall	0.91 (0.03 to 1.79) **8**		0.97 (0.59 to 1.34) **8**	0.89 (0.40 to 1.39) **8**
Insoluble and overall		No data	No data	No data
	Summary estimate	Summary estimate	Summary estimate	Global estimate
	0.58 (0.42 to 0.73) **196**	0.63 (0.48 to 0.79) **166**	0.79 (0.49 to 1.08) **66**	0.66 (0.54 to 0.78) **276**

Table 4.11: Summary of the solubility of amyloid beta 40. Soluble, insoluble, total and combined estimates of effects size are given. The end column represents the combined effect size across all solubilities and the end row provides summary estimate for each solubility.

Likewise, I explored estimates of effect regarding the solubility of amyloid beta 42. Sufficient were present to examine the relationship between soluble and insoluble species (144 experiments) however few data reported other combinations: (Table 4.12).

	Soluble Effect size (95% CI) and N	**Insoluble** Effect size (95% CI) and N	**Overall** Effect size (95% CI) and N	**Combined** Effect size (95% CI) and N
Soluble only	0.93 (0.51 to 1.36) **36**			0.93 (0.51 to 1.36) **36**
Insoluble only		0.89 (0.6 to 1.17) **42**		0.89 (0.6 to 1.17) **42**
Overall			1.02 (0.69 to 1.35) **66**	1.02 (0.69 to 1.35) **66**
Soluble and insoluble	0.58 (0.39 to 0.77) **144**	0.63 (0.46 to 0.81) **144**		0.63 (0.48 to 0.78) **144**
Soluble and overall	0.91 (-0.1 to 1.91) **6**		0.85 (0.4 to 1.3) **6**	0.89 (0.26 to 1.53) 6
Insoluble and overall		0.45 (-0.07 to 0.97) **3**	0.43 (-0.05 to 0.91) **3**	0.44 (0.08 to 0.79) **3**
	Summary estimate	**Summary estimate**	**Summary estimate**	**Global estimate**
	0.56 (0.4 to 0.72) **187**	0.63 (0.47 to 0.79) **162**	0.55 (0.26 to 0.83) **52**	0.76 (0.64 to 0.88) **295**

Table 4.12: Summary of the solubility of amyloid beta 42. Soluble, insoluble, total and combined estimates of effects size are given. The end column represents the combined effect size across all solubilities and the end row provides summary estimate for each solubility.

Amyloid beta total

Finally, I explored estimates of efficacy by solubility within total amyloid beta levels. Experiments were most likely to report the overall level of amyloid regardless of solubility (31 experiments) and there were too few data to allow comparison of soluble and total amyloid (6 experiments) or insoluble and total amyloid beta (1 experiment). There were however sufficient data to examine the relationship between soluble and insoluble species of total amyloid beta (18 experiments, Table 4.13).

	Soluble Effect size (95% CI) and N	**Insoluble** Effect size (95% CI) and N	**overall** Effect size (95% CI) and N	**Combined** Effect size (95% CI) and N
Soluble only	0.68 (-0.78 to 2.15) **1**			0.68 (-0.78 to 2.15) **1**
Insoluble only		0.24 (-1.11 to 1.59) **3**		0.24 (-1.11 to 1.59) **3**
Overall only			0.95 (0.61 to 1.29) **35**	0.95 (0.61 to 1.29) **35**
Soluble and insoluble	0.65 (0.23 to 1.08) **16**	1.22 (0.51 to 1.93) **16**		0.85 (0.38 to 1.32) **16**
Soluble and overall	0.06 (-0.57 to 0.7) **8**		0.09 (-0.63 to 0.81) **8**	0.14 (-0.17 to 0.45) **8**
Insoluble and overall		0.65 (0.04 to 1.25) **3**	0.57 (0.12 to 1.01) **3**	0.47 (-0.22 to 1.16) **3**
	Summary estimate	**Summary estimate**	**Summary estimate**	**Global estimate**
	0.5 (0.12 to 0.87) **23**	1.01 (0.43 to 1.59) **20**	0.79 (0.5 to 1.09) **44**	0.75 (0.52 to 0.99) **62**

Table 4.13: Summary of the solubility of amyloid beta 40. Soluble, insoluble, total and combined estimates of effects size are given. The end column represents the combined effect size across all solubilities and the end row provides summary estimate for each solubility.

4.2.4 Relationships between different solubilities of amyloid

For the 144 studies which measured both changes in soluble and insoluble amyloid beta 40 I performed meta-regression to identify potential relationships. Data suggested that changes in soluble amyloid could explain a significant proportion of the changes in insoluble amyloid (adjusted R^2 value of 0.59, $p<0.02$, Figure 4.11, Table 4.14). Similarly, 144 experiments suggested that changes in soluble amyloid beta 42 could explain 35.3 of changes in insoluble amyloid beta 42 (Figure 4.12, Table 4.14, $p<0.02$). For amyloid beta total, 16 experiments suggested that 62.9% of changes in insoluble amyloid could be explained by changes in soluble amyloid (Figure 4.13, Table 4.14, $p<0.02$)

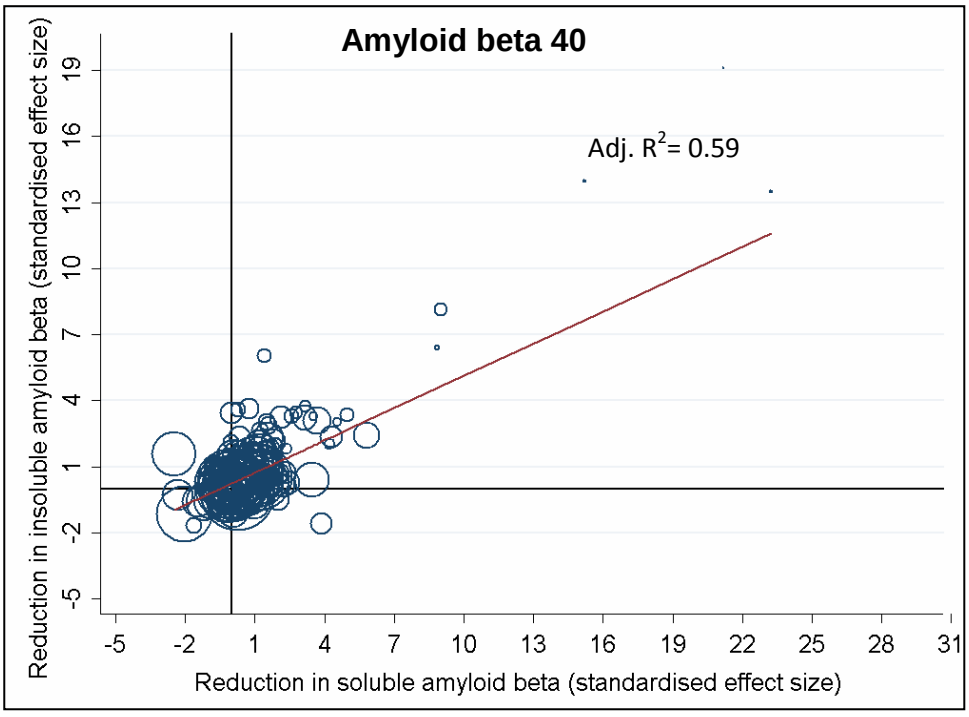


Figure 4.11: I performed meta-regression in order to investigate the relationship between changes in soluble and insoluble amyloid beta 40. Symbol size denotes the inverse of the variance for each estimate of effect size.

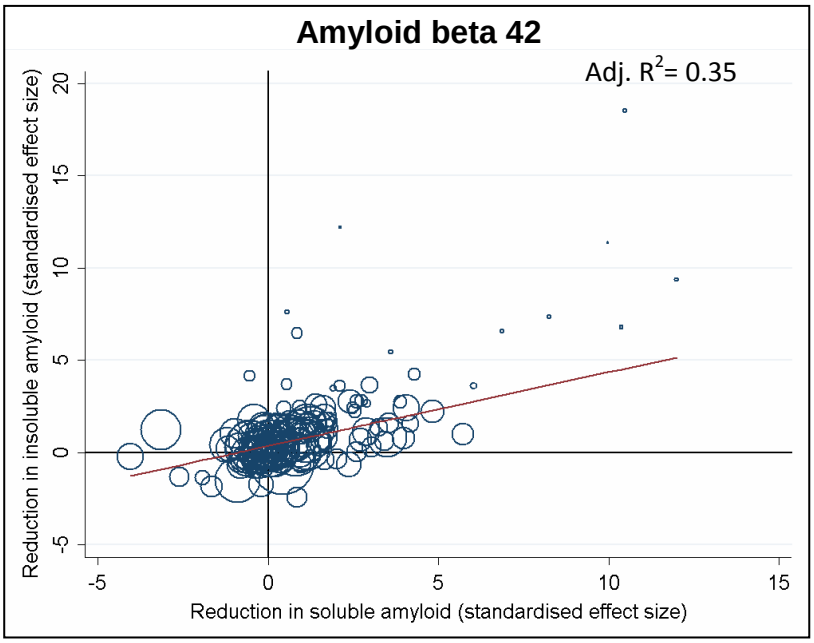


Figure 4.12: I performed meta-regression in order to investigate the relationship between changes in soluble and insoluble amyloid beta 42. Symbol size denotes the inverse of the variance for each estimate of effect size.

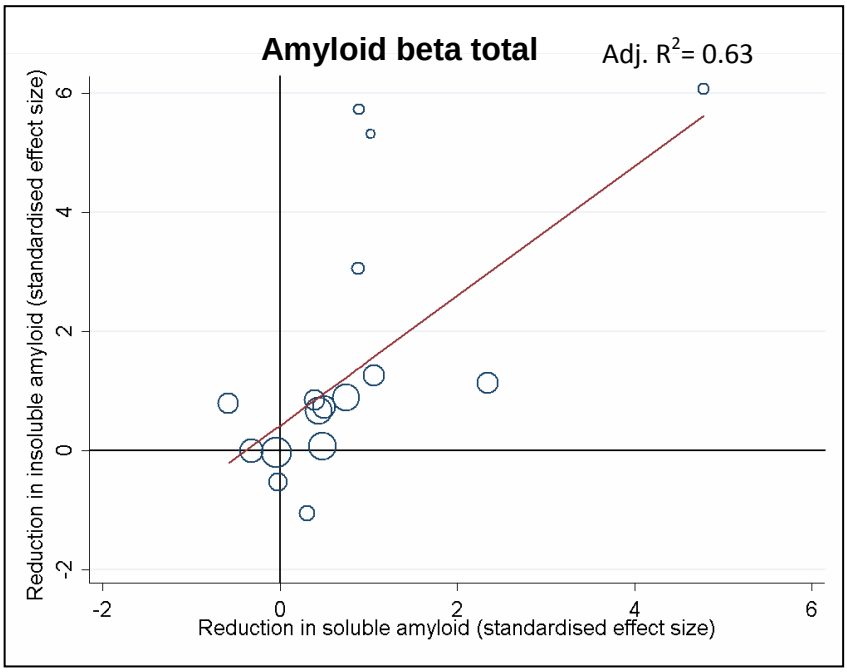


Figure 4.13: I performed meta-regression in order to investigate the relationship between changes in soluble and insoluble amyloid beta total. Symbol size denotes the inverse of the variance for each estimate of effect size.

	Co-efficient (SMD ES)	Standard error	τ	P>|t| **where α=0.02**	Lower 95% CI	Upper 95 CI%	N	Adj. R^2
Sol. 40 vs. Insol. 40	0.489	0.0568	8.6	0	0.3763	0.601	144	0.59
Sol. 42 vs. Insol. 42	0.400	0.0568	7.06	0	0.288	0.512	144	0.35
Sol. total vs. Insol. total	1.087	0.346	3.14	0.007	0.344	1.831	16	0.63

Table 4.14: Relationships between soluble and insoluble amyloid beta outcomes were analysed using meta-regression techniques. For each comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

4.2.5 Amyloid beta summary

In summary experiments were almost five times more likely to report amyloid beta 40 or amyloid beta 42 opposed to total amyloid. I observed that estimates of efficacy for amyloid differed according the transgenic group assessed, for data overall and more specifically within both amyloid beta 40 and amyloid beta 42. Collectively the data suggest that there may be a number of strong relationships between amyloid species, most prominently between changes in amyloid beta 40 and 42. As amyloid beta 40 and 42 datasets represented the majority of amyloid beta, I limit subsequent analyses on amyloid to these data only.

4.3 Tau neurofibrillary tangles

Eighty four experiments measured changes in tau (984 animals) where data suggested a baseline efficacy of 0.55 SD (0.38 to 0.72). I partitioned heterogeneity to assess whether estimates of tau overall or the phosphorylation state of tau differed where this accounted for a significant proportion (χ^2=10.0, p<0.05). Estimates suggested interventions were more effective at reducing overall levels of tau 0.60 SD (0.38 to 0.81) compared to improving the phosphorylation state of tau, 0.44 SD (0.20 to 0.69, Table 4.15).

	Overall Tau levels	Phosphorylation state of tau	Summary estimate*
Effect size	0.44	0.60	0.53
95 % CI	(0.20 to 0.69)	(0.38 to 0.81)	(0.36 to 0.69)
n	**59**	**53**	**112**

Table 4.15: Estimates of standardised effect size according to whether tau was measured quantatively or the phosphorylation state of tau was assessed. Brackets give 95 percent confidence limits and lower number indicates the number of experiments, *as different outcomes can be represented in the same cohort of animals some are represented more than once

Exploring data further, I identified 31 experiments which reported overall changes in tau without the phosphorylation state of tau whereas 25 experiments reported vice versa (Table 4.16). 28 experiments reported both overall tau and phosphorylated tau which was sufficient for meta-regression analysis (i.e. >10 outcomes).

	Tau Effect size (95% CI) and N	Phospho tau Effect size (95% CI) and N	All tau species Effect size (95% CI) and N
Overall tau only	1.10 (0.57 to 1.64) **31**		1.10 (0.57 to 1.64) **31**
Phosphorylation state of tau only		0.64 (0.31 to 0.97) **25**	0.64 (0.31 to 0.97) **25**
Both tau and phosphorylation state of tau	0.18 (-0.06 to 0.43) **28**	0.57 (0.29 to 0.85) **28**	0.40 (0.18 to 0.61) **28**
	Summary estimate	**Summary estimate**	**Global estimate**
	0.44 (0.2 to 0.69) **59**	0.60 (0.38 to 0.81) **53**	0.55 (0.38 to 0.72) **84**

Table 4.16: Estimates of standardised effect size according to each tau species assessed. Columns represent the different forms of tau reported, overall tau and phosphorylation state of tau (phosphorylated tau). End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments.

4.3.1 Tau outcomes and transgenic model group estimates

I partitioned heterogeneity for tau outcomes according to the transgenic model used which accounted for a significant proportion (χ^2=16.14, df=4, p<0.01). Estimates of efficacy were higher in the 'other' transgenic group; however wide confidence intervals and few limited our ability to identify associations (Table 4.17 and Figure 4.14).

Transgenic model Group	Tau Effect size (95% CI) and N	Phos. state of tau Effect size (95% CI) and N	Combined Effect size (95% CI) and N
APP	-0.65 (-1.34 to 0.05) **3**	0.62 (-0.08 to 1.31) **7**	0.03 (-0.39 to 0.45) **8**
APPPS	**no data**	1.05 (-0.24 to 2.34) **4**	1.05 (-0.24 to 2.34) **4**
3xTgAD	0.59 (0.27 to 0.9) **42**	0.45 (0.15 to 0.74) **29**	0.56 (0.32 to 0.81) **48**
Tau	0.41 (0.07 to 0.75) **14**	0.83 (0.43 to 1.23) **9**	0.63 (0.36 to 0.90) **20**
PS1	**no data**	**no data**	**no data**
Other	**no data**	1.33 (-0.13 to 2.79) **4**	1.33 (-0.13 to 2.79) **4**
	Summary estimate	**Summary estimate**	**Global estimate**
	0.44 (0.2 to 0.69) **59**	0.6 (0.38 to 0.81) **53**	0.55 (0.38 to 0.72) **84**

Table 4.17 Estimates of standardised effect size according to each transgenic model group used. Columns represent different tau species (overall tau and phosphorylation state of tau [Phospho tau]). End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. (N.B. some experiments may be represented more than once), phos. (phosphorylation).

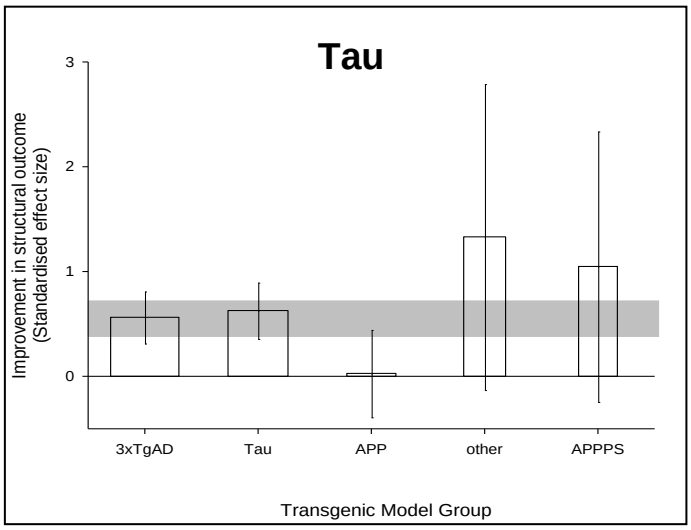
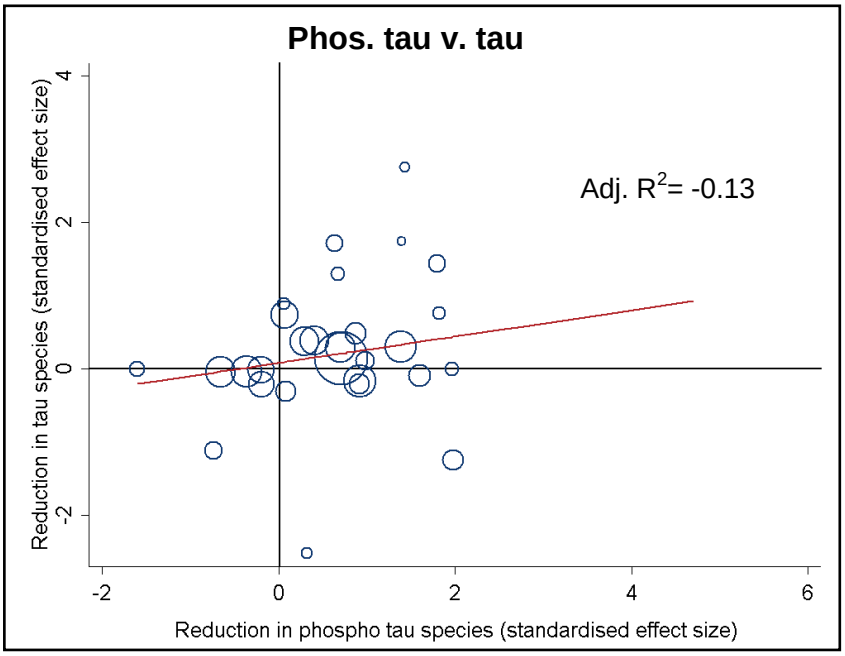


Figure 4.14: I stratified tau data according to transgenic model group used where this accounted for a significant proportion of the observed heterogeneity. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate and bar width represents the log of the number of animals.

4.3.2 Relationships within different tau species

For the 28 experiments which examined both tau and phosphorylated tau species I performed a meta-regression to identify potential relationships. Our analysis suggests that changes in the phosphorylation state of tau were not reflective of changes observed in overall tau (See Figure 4.15 and Table 4.18). The negative adjusted R squared value reflects data where variables explain less of the heterogeneity that I would expect by chance.



	Co-efficient (SMD ES)	Standard error	τ	P>|t| where α=0.05	Lower 95% CI	Upper 95 CI%	N	Adj. R^2
Phospho tau vs. tau	0.18	0.18	1.01	0.32	-0.19	0.55	28	-0.13

Figure 4.15 (upper) and Table 4.18 (lower): I investigated whether changes in the phosphorylation state of tau (phosphor tau) could explain a significant proportion of the changes in tau. Meta-regression output provides co-efficient, standard error, τ and the lower and upper 95% confidence limits of the co-efficient estimate alongside the number of experiments (N) and adjusted R squared (Adj. R^2).

4.3.3 Summary of tau species

Our analyses identified that estimates of efficacy for overall tau were smaller than estimates for the phosphorylation state of tau. The transgenic model group used I associated with differences in efficacy but these were for the most part subtle differences. In respect of the limited data I decided to include all tau when performing subsequent analyses.

4.4 Cell infiltrates

Eighty nine cellular infiltrate experiments (representing 1099 animals) suggested an overall reduction in cell infiltrates of 0.40 SD (0.13 to 0.68, 89 experiments). I partitioned heterogeneity in order to assess differences between cellular infiltrate species and identified smaller estimates of efficacy for microgliosis opposed to astrocytosis (χ^2=58.4, <0.05, Table 4.19).

	Astrocytosis assessed	Microgliosis assessed	Summary estimate*
Effect size	**1.07**	0.24	0.56
95% CI	(0.68 to 1.45)	(-0.08 to 0.56)	(0.31 to 0.81)
n	**43**	**72**	**115**

Table 4.19: Estimates of standardised effect size for astrocytosis and microgliosis overall and end column indicates the overall estimate. Brackets give 95 percent confidence limits and lower number indicates the number of experiments, *as different outcomes can be represented in the same cohort of animals some are represented more than once

I explored this dataset further (Table 4.20) and identified 17 experiments which examined astrocytosis in isolation, whereas 46 experiments examined microgliosis without astrocytosis. Twenty six experiments examined both astrocytosis and microgliosis meaning that meta-regression to identify potential relationships was possible.

	Astrocytosis **Effect size (95% CI) and N**	**Microgliosis** **Effect size (95% CI) and N**	**Combined** **Effect size and N (95% CI) and N**
Astrocytosis only	1.07 (0.66 to 1.48) **17**		1.07 (0.66 to 1.48) **17**
Microgliosis only		-0.37 (-0.70 to -0.04) **46**	-0.37 (-0.7 to -0.04) **46**
Both astrocytosis and microgliosis	1 (0.42 to 1.57) **26**	1.25 (0.79 to 1.72) **26**	1 (0.42 to 1.57) **26**
	Summary estimate	**Summary estimate**	**Global estimate**
	1.07 (0.68 to 1.45) **43**	0.24 (-0.08 to 0.56) **72**	0.40 (0.13 to 0.68) **89**

Table 4.20: Estimates of standardised effect size according to the different measures of cellular infiltrates assessed. Columns represent astrocytosis and microgliosis. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments.

4.4.1 Cellular infiltrates and transgenic model group estimates

I stratified cellular infiltrates overall by the transgenic mouse model group used but estimates were relatively similar and this did not account for a significant proportion of heterogeneity (Table 4.21, χ^2= 5.52). Similarly where I stratified astrocytosis outcomes this did not account for a significant proportion of the heterogeneity (Table 4.21, χ^2= 5.76). Where I stratified microgliosis outcomes according to the transgenic group used this did account for a significant proportion of the observed heterogeneity (Table 4.21, χ^2= 11.1) however for the majority of data (i.e. APP and APPPS transgenic groups) estimates were relatively similar.

Transgenic model Group	Astrocytosis Effect size (95% CI) and N	Microgliosis Effect size (95% CI) and N	Combined Effect size and N (95% CI) and N
APP	1.12 (0.58 to 1.65) **28**	0.15 (-0.24 to 0.54) **50**	0.34 (-0.02 to 0.7) **61**
APPPS	1.04 (0.41 to 1.67) **12**	0.36 **(-0.21 to 0.94)** **21**	0.51 (0.02 to 0.99) **25**
3xTgAD	1.02 (-0.16 to 2.2) **1**	2.69 (1.08 to 4.29) **1**	1.61 (0.65 to 2.56) **1**
Tau	0.26 (-0.55 to 1.08) **2**	**no data**	0.26 (-0.55 to 1.08) **2**
PS	**no data**	**no data**	**no data**
Other	**no data**	**no data**	no **data**
	Summary estimate	**Summary estimate**	**Global estimate**
	1.07 (0.68 to 1.45) **43**	0.24 (-0.08 to 0.56) **72**	0.40 (0.13 to 0.68) **89**

Table 4.21: Estimates of standardised effect size according to each transgenic model group used and the different measures of cellular infiltrates assessed. Columns represent astrocytosis and microgliosis. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. (N.B. some experiments may be represented more than once).

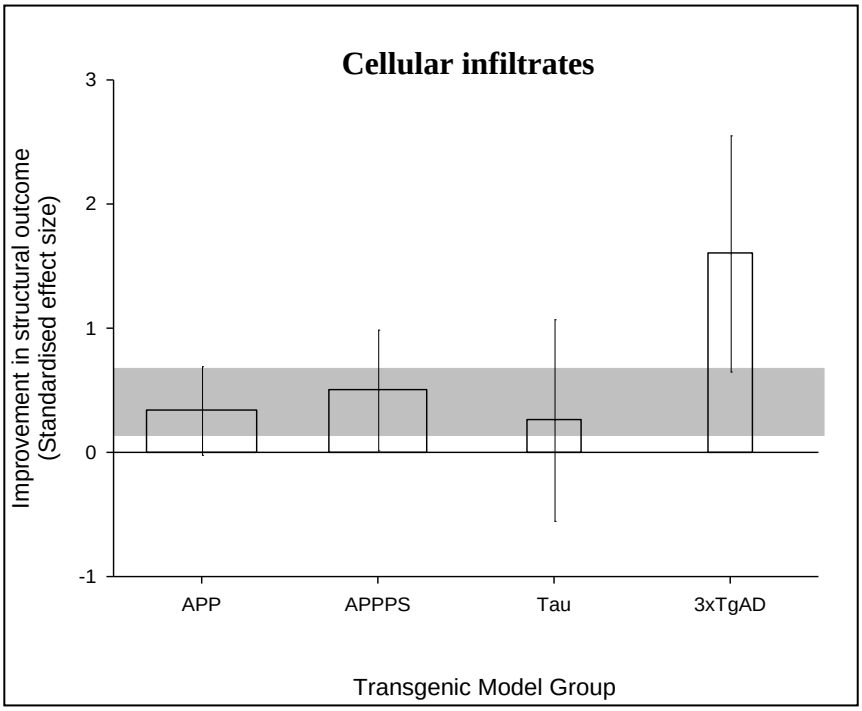
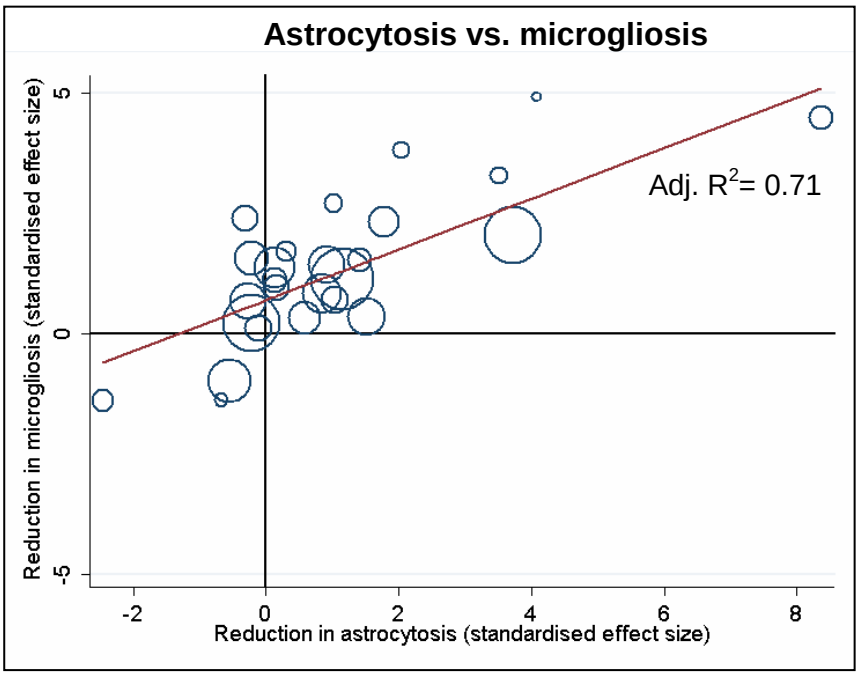


Figure 4.16: I stratified cellular infiltrate outcomes according to transgenic model group used where this did not account for a significant proportion of the observed heterogeneity. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.4.2 Relationships within cellular infiltrates

Subsequently, I performed meta-regression in order to further our understanding of the potential relationship between astrocytosis and microgliosis for the 26 cohorts which reported both. I found a relatively strong correlation (Adjusted R squared= 0.71, $p<0.05$) between changes in both outcomes (Figure 4.17 and Table 4.22)



	Co-efficient (SMD ES)	Standard error	τ	P>|t| **where α=0.01**	Lower 95% CI	Upper 95 CI%	N	Adj. R^2
Astrocytosis vs. microgliosis	0.527	0.094	5.58	0	0.332	0.722	26	0.71

Figure 4.17 & (upper) Table 4.22 (lower): Investigating the relationship between astrocytosis and microgliosis using meta-regression techniques. Symbol size denotes the inverse of the variance for each estimate of effect size. Meta-regression output describes co-efficient, standard error, t value and the lower and upper 95% confidence limits of the co-efficient estimate.

4.4.3 Summary of cellular infiltrates

Our analyses at both the global level and transgenic model level suggested differences between intervention estimates on astrocytosis and microgliosis, however changes in astrocytes were generally good predictors of changes in microgliosis. I took both outcomes forward together as 'cellular infiltrates' to maximise statistical power.

4.5 Neurodegeneration

Sixty four neurodegeneration experiments representing 962 animals suggested an overall improvement of 0.91 SD ([0.69 to 1.12], χ^2= 192). I partitioned heterogeneity in order to assess whether assessing direct or indirect neurodegeneration outcomes impacted on observed outcome and found that this accounted for a significant proportion of the observed heterogeneity (χ^2=6.80, p<0.05). I observed smaller estimates of effect size for direct measures of neurodegeneration opposed to indirect measures 0.59 SD ([0.22 to 0.97], vs. 1.03 SD ([0.78 to 1.13], see Table 4.23).

	Direct measures	Indirect measures	Summary estimate*
Effect size	0.60	1.03	0.91
95% CI	(0.22 to 0.97)	(0.78 to 1.29)	(0.69 to 1.12)
n	**22**	**42**	**64**

Table 4.23: Estimates of standardised effect size according to measures of neurodegeneration were direct or indirect. End column indicates summary estimate, Brackets give 95 percent confidence limits and lower number indicates the number of experiments, *as no experiments examined both measures animals are not represented more than once.

I explored this dataset further and calculated estimates of efficacy wherever, indirect, direct or both were reported and identified that no experiments examined both direct and indirect measures (Table 4.24).

4.5.1 Neurodegeneration and transgenic model group estimates

I stratified data overall according to the transgenic mouse model used but this did not account for a significant proportion of the observed heterogeneity (χ^2=9.51, Table 4.25 and Figure 4.17).

	Direct Effect size (95% CI) and N	Indirect Effect size (95% CI) and N	Combined Effect size (95% CI) and N
Direct only	0.60 (0.22 to 0.97) **22**		0.60 (0.22 to 0.97) **22**
Indirect only		1.03 (0.78 to 1.29) **42**	1.03 (0.78 to 1.29) **42**
Both direct and indirect	No data	No data	No data
	Summary estimate	**Summary estimate**	**Global estimate**
	0.60 (0.22 to 0.97) **22**	1.03 (0.78 to 1.29) **42**	0.91 (0.69 to 1.12) **64**

Table 4.24: Estimates of standardised effect size according to the different combinations of neurodegeneration measures reported. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments.

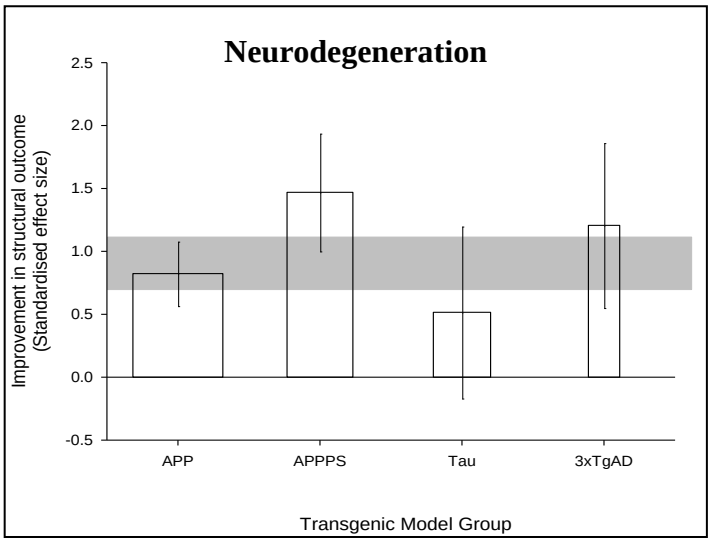


Figure 4.18(previous page): I stratified cellular infiltrate outcomes according to transgenic model group used. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

Transgenic model Group	Direct Effect size (95% CI) and N	Indirect Effect size (95% CI) and N	Combined Effect size and N (95% CI) and N
APP	0.41 (-0.02 to 0.85) **12**	0.98 (0.67 to 1.28) **31**	0.82 (0.57 to 1.08) **43**
APPPS	1.62 (0.91 to 2.33) **4**	1.42 (0.8 to 2.04) **7**	1.47 (1 to 1.94) **11**
3xTgAD	**No data**	1.21 (0.55 to 1.86) **1**	1.21 (0.55 to 1.86) **1**
Tau	0.35 (-0.43 to 1.12) **7**	0.77 (-0.5 to 2.05) **3**	0.52 (-0.13 to 1.18) **10**
PS1	**No data**	**No data**	**No data**
Other	**No data**	**No data**	**No data**
	Summary estimate	**Summary estimate**	**Global estimate**
	0.59 (0.22 to 0.97) **23**	1.03 (0.78 to 1.29) **42**	0.91 (0.69 to 1.12) **65**

Table 4.25: Estimates of standardised effect size according to each transgenic model group used and the different measures of neurodegeneration assessed. Columns represent direct and indirect measures. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. (N.B. some experiments are represented more than once).

4.5.2 Relationships within neurodegeneration outcomes

No experiments examined both direct and indirect measures of neurodegeneration thus I could not investigate relationships.

4.5.3 Summary of neurodegeneration outcomes

I identified that interventions successfully improved neurodegeneration overall and also specifically within direct and indirect outcome measures. Where I stratified data according to whether data were direct or indirect measures, indirect measures were associated with higher estimates of efficacy. I did not identify a significant impact of the transgenic model group used.

4.6 Summary of pathological outcomes and potential relationships

Improving our understanding of how different pathologies are connected in transgenic mouse models would be an asset to translational research. Across all pathological outcomes included I identified 725 experimental cohorts which had a global improvement of 0.78 SD (0.71 to 0.65, Table 4.26).

I then inspected how much data were present across different pathological outcomes within the same cohort of transgenic mice (Table 4.27). Overall I identified sufficient data (i.e. >10 experiments) for 12 other relationships to be investigated, however the relationship between amyloid beta 40 and 42 (334 experiments) had been investigated previously in section 4.2.2.

	Plaque burden	Amyloid beta 40	Amyloid beta 42	Tau	Cellular infiltrates	Neurodegeneration	Global estimate
Effect size	0.98	0.68	0.78	0.55	0.40	0.91	0.78
95% CI	(0.87 to 1.1)	(0.57 to 0.79)	(0.67 to 0.88)	(0.38 to 0.72)	(0.13 to 0.68)	(0.69 to 1.12)	(0.71 to 0.85)
n	**378**	**388**	**389**	**84**	**89**	**64**	**725**

Table 4.26: Estimates of standardised effect size according to the different measures of neurodegeneration assessed. Columns represent direct and indirect measures. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments.

Plaque burden ES (95% CI) and N	**Amyloid beta 40** ES (95% CI) and N	**Amyloid beta 42** ES (95% CI) and N	**Tau** ES (95% CI) and N	**Cellular infiltrates** ES (95% CI) and N	**Neurode-generation** ES (95% CI) and N	**Combined estimate** ES (95% CI) and N
0.89 (0.7 to 1.09) **145***	0.72 (0.7 to 1.09) **145***					0.81 (0.65 to 0.97) **145**
0.84 (0.67 to 1.01) **165***		0.84 (0.74 to 1.1) **165***				0.88 (0.72 to 1.03) **165**
1.28 (0.69 to 1.88) **30***			0.73 (0.31 to 1.14) **30***			0.94 (0.55 to 1.33) **30**
1.18 (0.92 to 1.44) **62***				0.65 (0.32 to 0.99) **61***		0.78 (0.53 to 1.03) **62**
1.18 (0.85 to 1.51) **29***					0.89 (0.62 to 1.16) **29***	0.99 (0.75 to 1.23) **29**
	(Previously reported) **334**					Previously reported **334**
	0.42 (0.06 to 0.78) **33***		0.40 (0.13 to 0.66) **33***			0.38 (0.15 to 0.61) **33**
	0.79 (0.51 to 1.07) **32***			0.94 (0.51 to 1.36) **32***		0.87 (0.56 to 1.18) **32**
	0.82 (0.37 to 1.28) **12***				1.11 (0.58 to 1.64) **12***	0.89 (0.56 to 1.22) **12**
		0.47 (0.13 to 0.81) **32***	0.33 (0.08 to 0.58) **32***			0.34 (0.13 to 0.55) **32**
		0.79 (0.51 to 1.07) **35***		0.94 (0.54 to 1.34) **35***		0.84 (0.55 to 1.14) **35**
		0.95 (0.5 to 1.41) **19***			1.11 (0.77 to 1.45) **19***	1 (0.7 to 1.3) **19**
			0.49 (0.03 to 0.95) **1**	1.61 (0.65 to 2.56) **1**		0.71 (0.29 to 1.12) 1
			-0.09 (-0.71 to 0.53) **8**		1.04 (0.57 to 1.52) **8**	0.33 (-0.08 to 0.74) **8**
				0.67 (0.43 to 0.92) **13***	1.13 (0.64 to 1.62) **13***	0.92 (0.58 to 1.25) **13**
Total	**Total**	**Total**	**Total**	**Total**	**Total**	**Global estimate**
0.98 (0.87 to 1.1) **378**	**0.68** (0.57 to 0.79) **388**	**0.78** (0.67 to 0.88) **389**	**0.55** (0.38 to 0.72) **84**	**0.4** (0.13 to 0.68) **89**	**0.91** (0.69 to 1.12) **64**	0.78 (0.71 to 0.85) **725**

Table 4.27: Estimates of standardised effect size where single cohorts were used to assess more than one pathological outcome. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. (N.B. some experiments are represented more than once).

4.6.1 Relationships between different pathological outcomes

I identified four statistically significant relationships of the 12 analyses, all of which involved plaque burden (where α= 0.004, Table 4.28, Figures 4.19 to 4.30). 145 experiments suggested that changes in amyloid beta 40 could explain a significant proportion (18.6%) of changes in plaque burden and similarly 165 experiments suggested that 19.1% of changes in amyloid beta 42 could explain changes in plaque burden. Changes in plaque burden were suggested to change 53.79% of changes in tau alongside 83.1% of changes in neurodegeneration. All other analyses proved statistically insignificant.

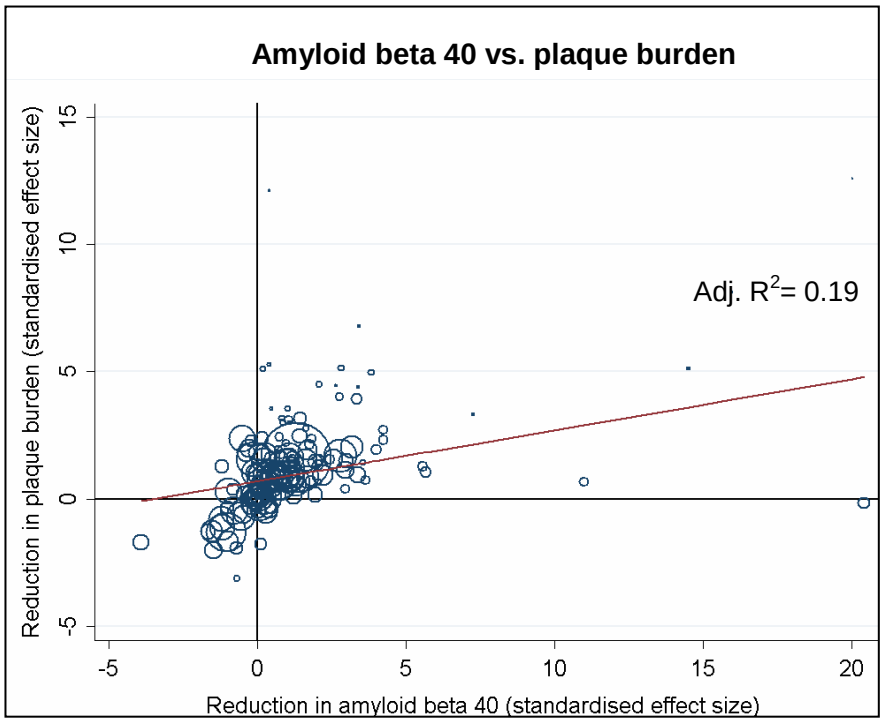


Figure 4.19: Changes in amyloid beta 40 could explain a significant proportion of changes in plaque burden. Symbol size denotes the inverse of the variance for each estimate of effect size.

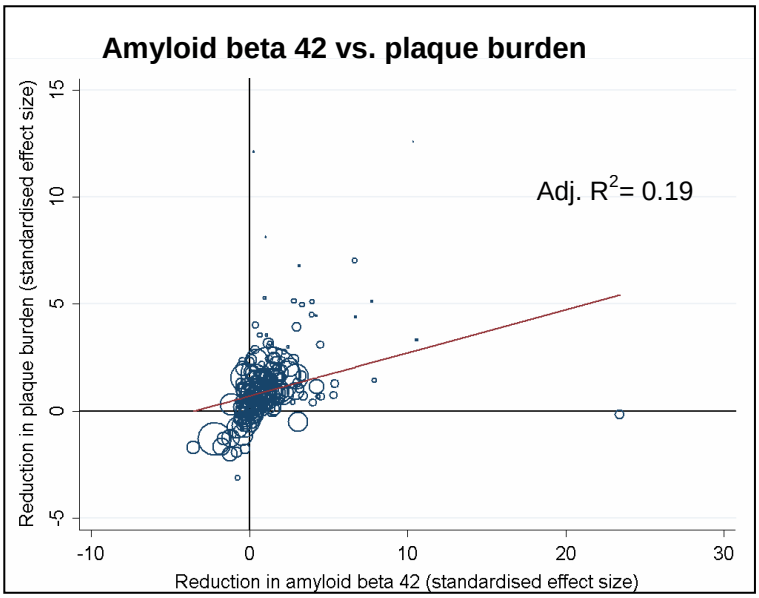


Figure 4.20: Changes in amyloid beta 42 could explain a significant proportion of changes in plaque burden. Symbol size denotes the inverse of the variance for each estimate of effect size

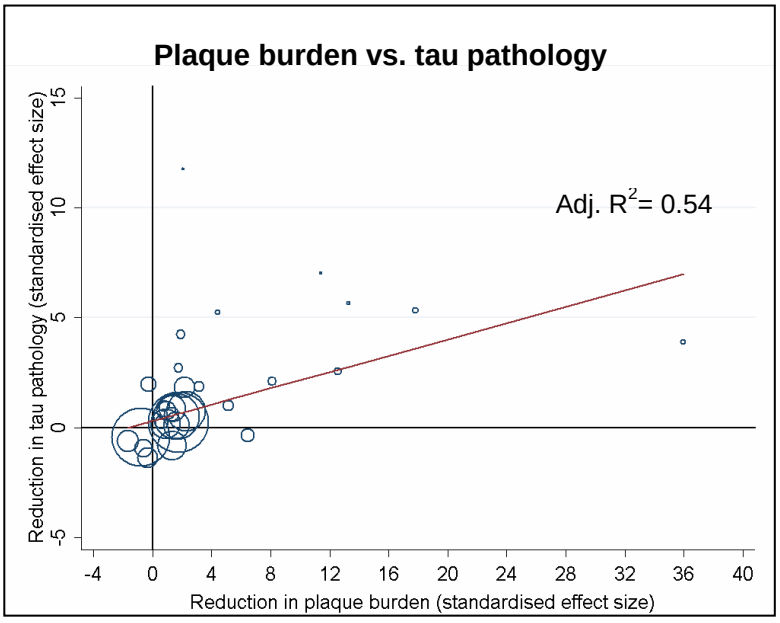


Figure 4.21: Changes in plaque burden could explain a significant proportion of changes in tau pathology. Symbol size denotes the inverse of the variance for each estimate of effect size.

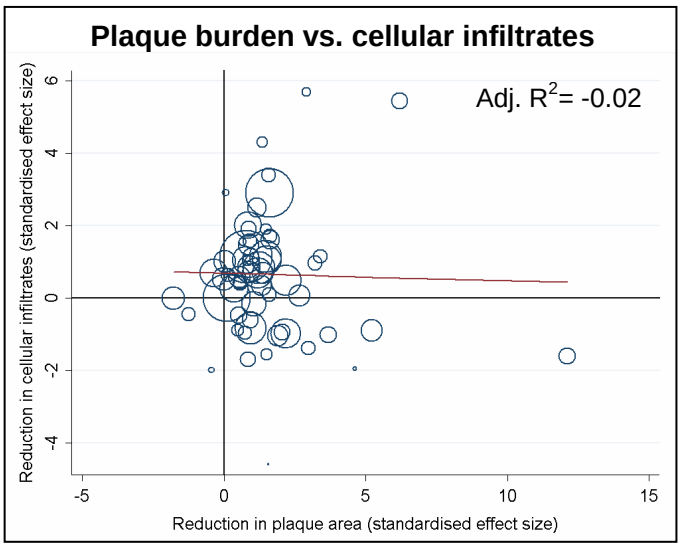


Figure 4.22: Changes in plaque burden could explain changes in cellular infiltrates. Symbol size denotes the inverse of the variance for each estimate of effect size

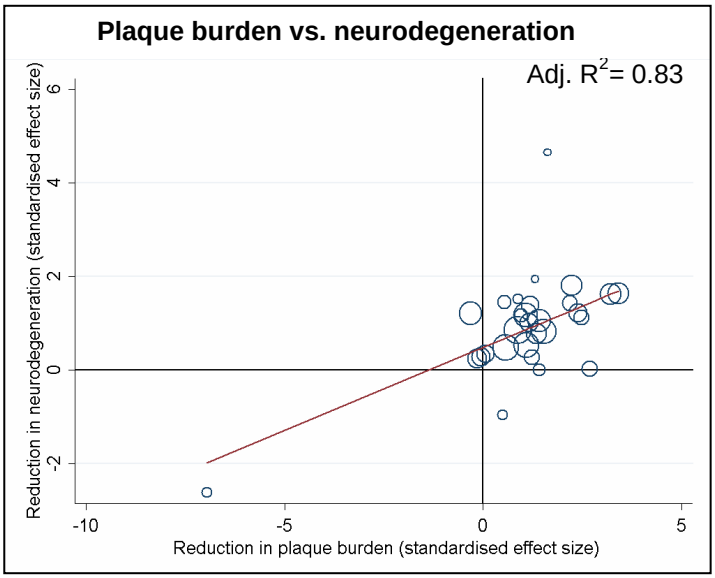


Figure 4.23: Changes in plaque burden could explain a significant proportion of changes in neurodgeneration. Symbol size denotes the inverse of the variance for each estimate of effect size

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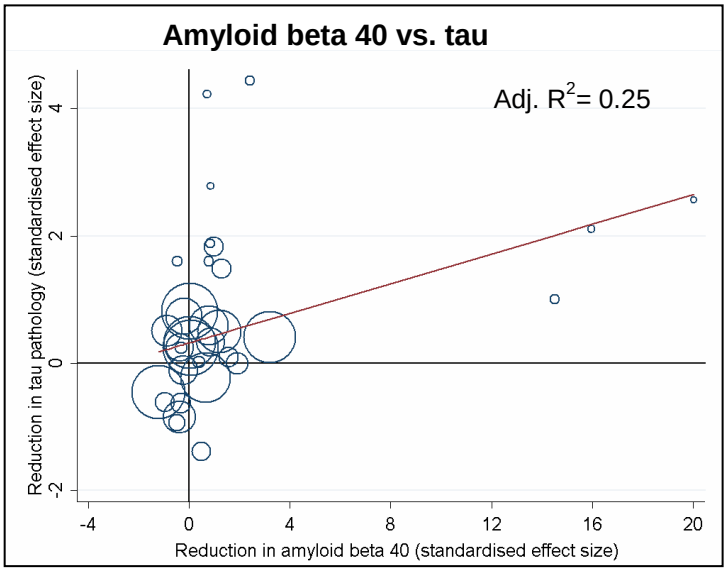


Figure 4.24: Changes amyloid beta 40 did not explain a statistically significant proportion of changes in tau. Symbol size denotes the inverse of the variance for each estimate of effect size

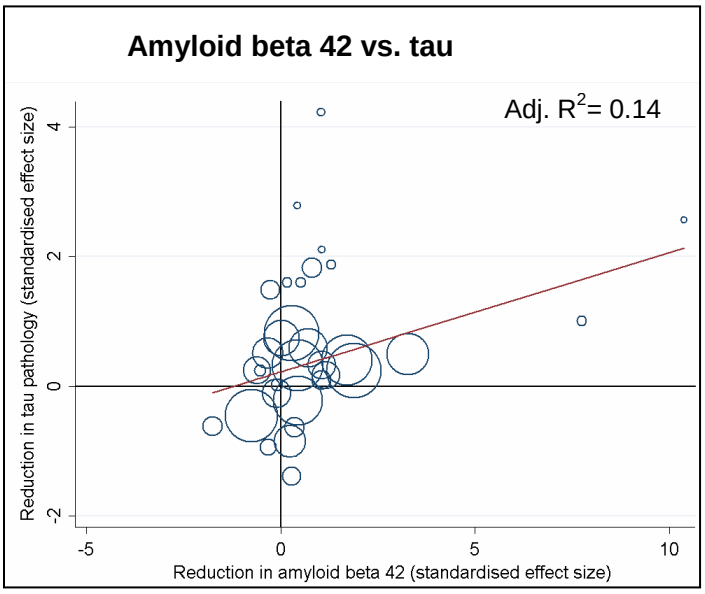


Figure 4.25: Changes amyloid beta 42 did not explain a statistically significant proportion of changes in tau. Symbol size denotes the inverse of the variance for each estimate of effect size

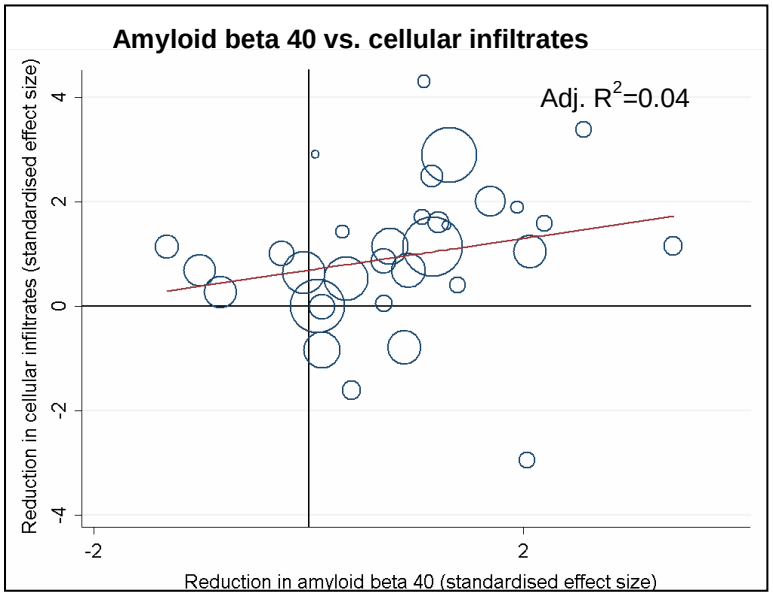


Figure 4.26: Changes amyloid beta 40 did not explain a statistically significant proportion of changes in cellular infiltrates. Symbol size denotes the inverse of the variance for each estimate of effect size

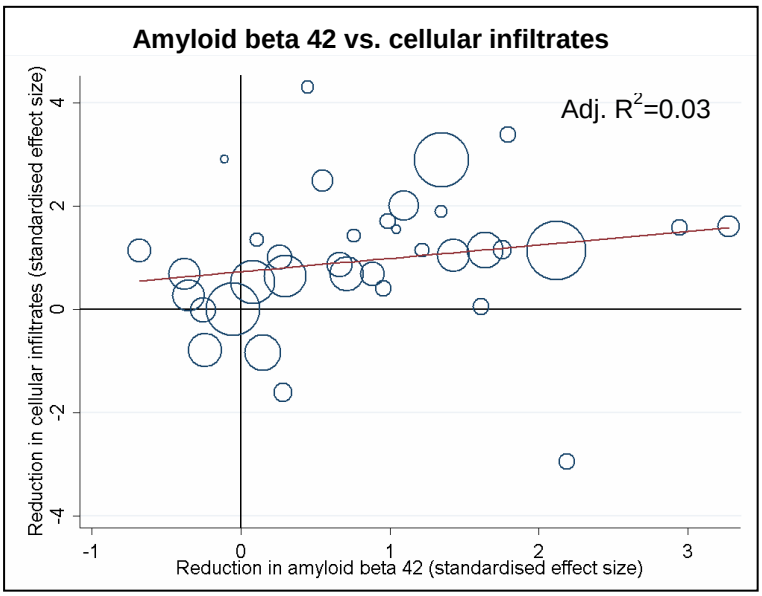


Figure 4.27: Changes amyloid beta 42 did not explain a statistically significant proportion of changes in cellular infiltrates. Symbol size denotes the inverse of the variance for each estimate of effect size

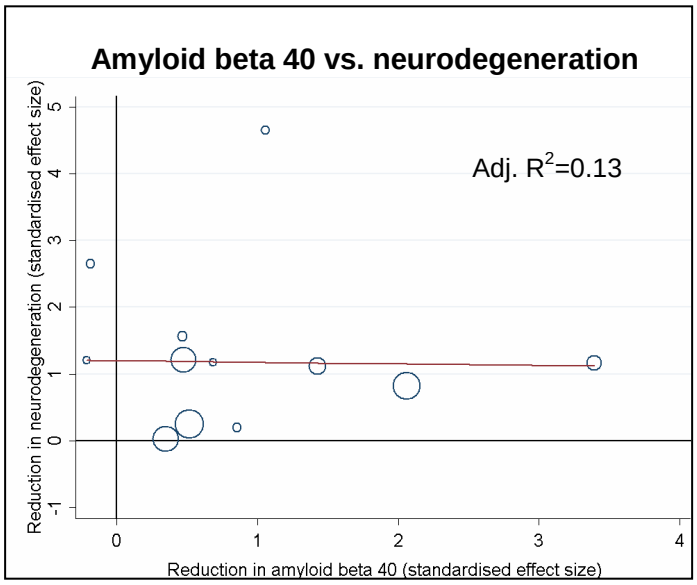


Figure 4.28: Changes amyloid beta 40 did not explain a statistically significant proportion of changes in neurodegeneration. Symbol size denotes the inverse of the variance for each estimate of effect size

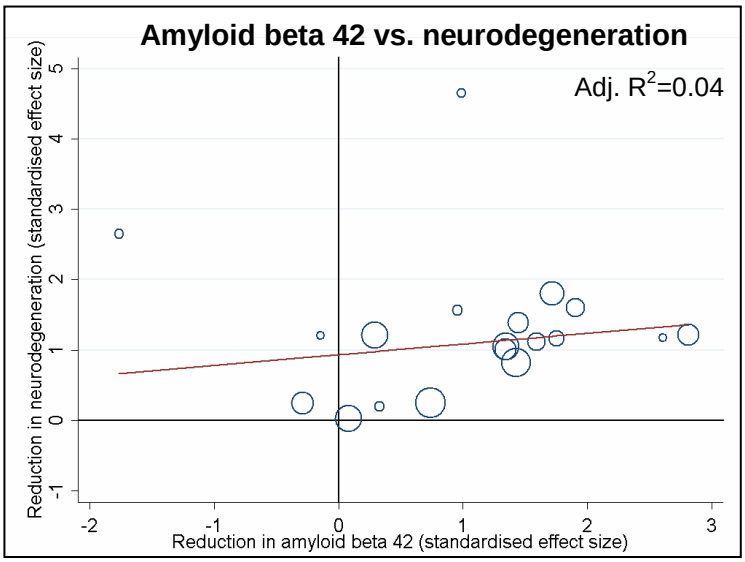


Figure 4.29: Changes amyloid beta 42 did not explain a statistically significant proportion of changes in neurodegeneration. Symbol size denotes the inverse of the variance for each estimate of effect size

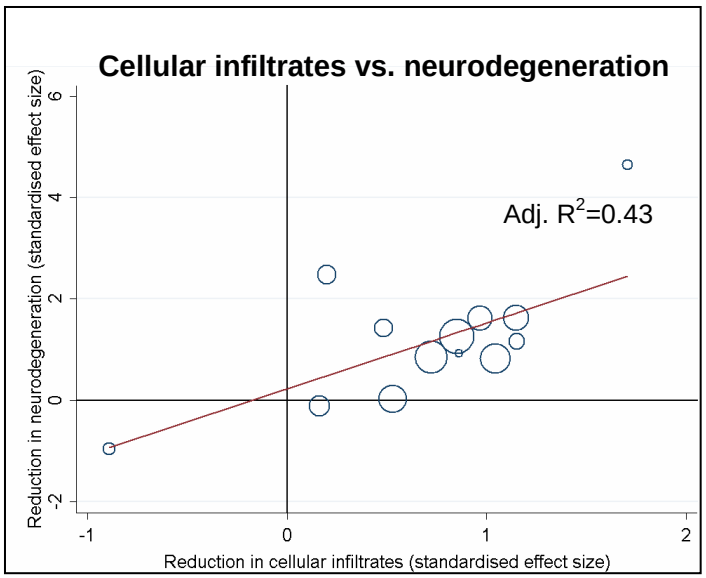


Figure 4.30: Changes amyloid beta 42 did not explain a statistically significant proportion of changes in neurodegeneration. Symbol size denotes the inverse of the variance for each estimate of effect size

	Co-efficient (SMD Effect size)	Standard Error	t	P>|t| where α=0.004	Lower 95% CI	Upper 95% CI	N	Adj. R^2
Aβ 40 vs. plaques	0.201	0.046	4.41	0	0.111	0.291	145	0.19
Aβ 42 vs. plaques	0.202	0.044	4.56	0	0.114	0.289	165	0.19
Plaques vs. tau	0.186	0.057	3.25	0.003	0.069	0.303	30	0.54
Plaques vs. cell Infiltrates	-0.021	0.104	-0.2	0.845	-0.229	0.188	61	-0.02
Plaques vs. neurod.	0.48	0.153	3.14	0.004	0.166	0.794	29	0.83
Aβ 40 vs. tau	0.117	0.056	2.08	0.046	0.002	0.231	33	0.25
Aβ 42 vs. tau	0.184	0.100	1.84	0.075	-0.02	0.388	32	0.14
Aβ 40 vs. cell Infiltrates	0.694	0.311	2.23	0.033	0.059	1.328	32	0.04
Aβ 42 vs. cell Infiltrates	0.259	0.239	1.08	0.287	-0.227	0.745	35	0.03
Aβ 40 vs. neurod.	-0.023	0.354	-0.07	0.949	-0.811	0.765	12	-0.24
Aβ 42 vs. neurod.	0.152	0.206	0.74	0.47	-0.282	0.586	29	0.13
Cell infiltrates vs. neurod.	1.304	0.482	2.71	0.02	0.244	2.364	13	0.43

Table 4.28: Summary of meta-regression data inspecting relationships between pathological outcomes. For each comparison co-efficient is given (in terms of standardised mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and adjusted R^2 (Adj. R^2)

Neurobehavioural outcomes

For calculating the effect size of neurobehavioural paradigms I inspected weighted mean difference estimates where I identified a number of extreme effect sizes. At the individual outcome level, estimates of neurobehavioural effect estimates of effect ranged from -8600% to 1113% and 29.5% of estimates calculated worsening or improvement greater than 100% (Figure 4.31). I identified that this effect was caused by the close approximation of means in wild type and control transgenic mice, therefore representing a weaknesses in the NMD approach. While this may raise concerns about the neurobehavioural impact of transgenes (see Chapter 5) I could not alter the dataset without introducing potential bias and thus could not use the normalised mean difference approach.

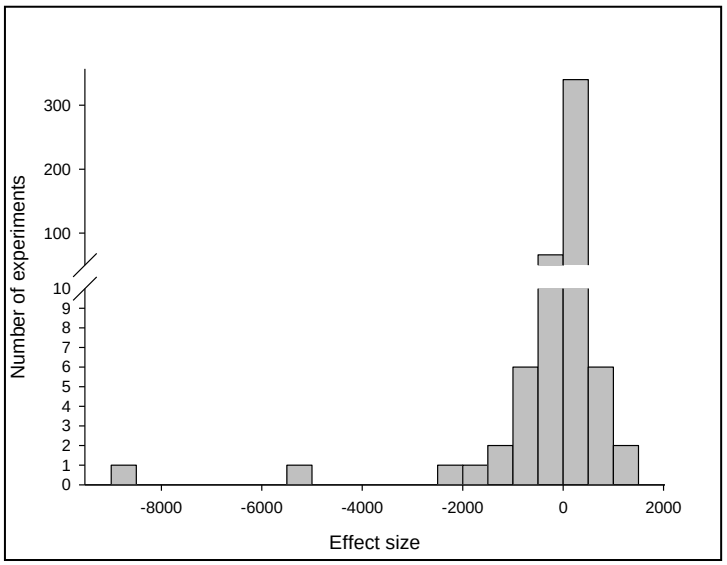


Figure 4.31: Histogram of normalised mean difference effect sizes for neurobehavioural data. While the majority of data lay between 100% improvement or worsening, 29.5% of pre-nested data lay outside such values.

As data were not similar enough to use difference in means estimates, I chose to perform analyses using standardised mean difference estimates. Therefore from the 259 neurobehavioural experiments identified (representing 4325 animals) I estimated that interventions improved outcomes by 0.61 SD (0.54 to 0.69). I explored each of the individual paradigms used within this estimate which are summarised in Table 4.29.

	Acquisition phase	Probe phase	RAWM Effect size	Fear conditioning	NORT	T /Y-maze Effect size
Effect size	0.49	0.63	0.86	0.70	0.95	0.46
95% CI	(0.4 to 0.58)	(0.5 to 0.76)	(0.61 to 1.10)	(0.51 to 0.89)	(0.63 to 1.27)	(0.21 to 0.71)
n	**130**	**113**	**41**	**45**	**25**	**28**

Table 4.29: I calculated estimates of effect in standardised effect size according to each paradigm used. Brackets represents 95% confidence limit and n represents the number of experiments

4.7 Acquisition phase of the Morris water maze

Overall, I estimated from 130 experiments that interventions improved neurobehavioral deficits in acquisition phase of the MWM by 0.49 SD (0.40 to 0.58).

4.7.1 Acquisition phase and transgenic model group estimates

I first stratified data according to the transgenic model group used which did not account for a significant proportion of heterogeneity (χ^2 =1.13, Figure 4.32, Table 4.30). Estimates of effect were broadly similar across all transgenic model groups.

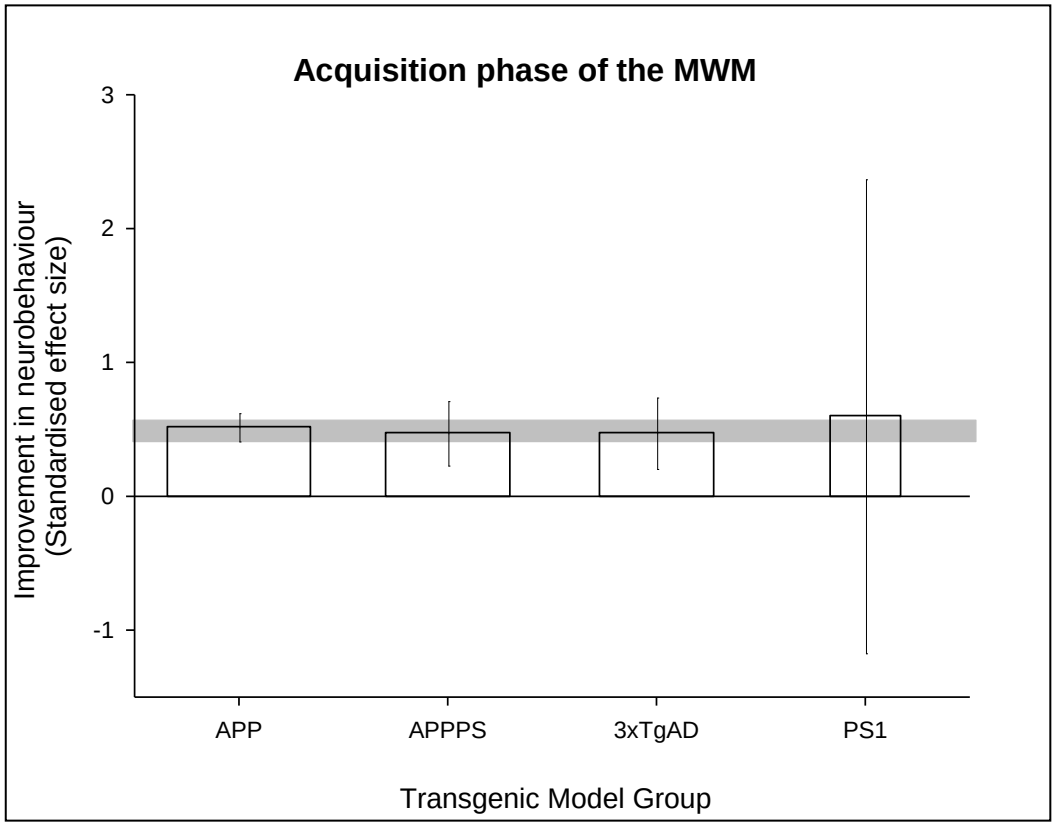


Figure 4.32: I stratified acquisition data according to transgenic model group used. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

APP Effect size (95% CI) and N	APPPS Effect size (95% CI) and N	3xTgAD Effect size (95% CI) and N	PS1 Effect size (95% CI) and N	GLOBAL Effect size (95% CI) and N
0.52 (0.42 to 0.63) 86	0.48 (0.23 to 0.72) 22	0.48 (0.21 to 0.74) 20	0.57 (-1.13 to 2.28) 2	0.49 (0.41 to 0.58) 130

Table 4.30: Estimates of efficacy according to the transgenic mouse model group used. Estimates are given in Standardised mean difference estimates (SD), brackets represent 95% confidence limits of this estimate and N represents the number of experiments.

4.7.2 Stratified acquisition phase analyses

Experiments performed within the acquisition phase of the MWM varied in terms of the size of the pool, temperature of water used and the total number of trials. I performed stratified analyses on each of these to gain estimates of effect size for each quartile. For acquisition outcomes I stratified estimates of effect according to the size of the pool used (109 experiments) but I did not identify a relationship between pool size and intervention effect (Figure 4.33a, (χ^2 =4.16). For outcomes where the pool temperature was stated (76 experiments) I again stratified estimates of effect but this did not account for a significant proportion of the observed heterogeneity (χ^2=3.03, Figure 4.33b). Where I could calculate the total number of trials (109 experiments) I found higher effect sizes associated with fewer total trials but this did not explain a significant proportion of the observed heterogeneity (χ^2=2.43, Figure 4.33c).

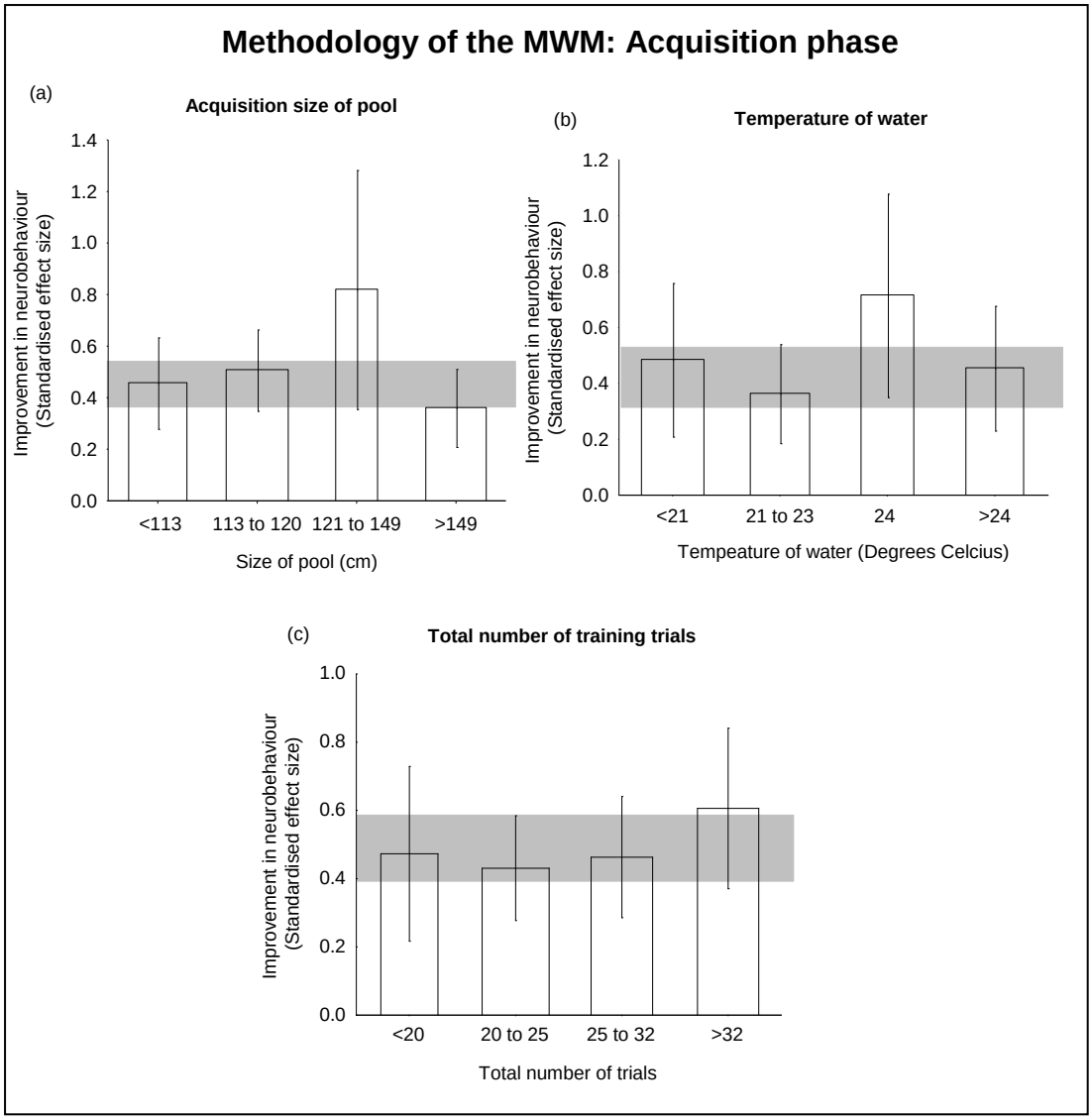


Figure 4.33: I stratified acquisition data according to the size of the pool used (a), temperature of water (b) and total number of training trials (c). Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.7.3 Summary of acquisition phase of the Morris water maze

Overall, I found that interventions successfully improved deficits in the acquisition phase of the MWM. Stratifying data according to the transgenic model used accounted for a significant proportion of the observed heterogeneity but this was not reflected by differences in estimates of effect. Stratifying data by size of pool, water temperature used or total number of training trials did not explain a significant proportion of the heterogeneity.

4.8 Probe phase of the Morris water maze

Overall, 113 experiments suggested that interventions successfully improved neurobehavioral deficits in the MWM by 0.63 SD, (0.50 to 0.76).

4.8.1 Probe phase and transgenic model group estimates

I first stratified data according to the transgenic model group used where estimates of effect were broadly similar and this did not account for a significant proportion of the observed heterogeneity (χ^2 =8.86, df=5, Figure 4.29, Table 4.31).

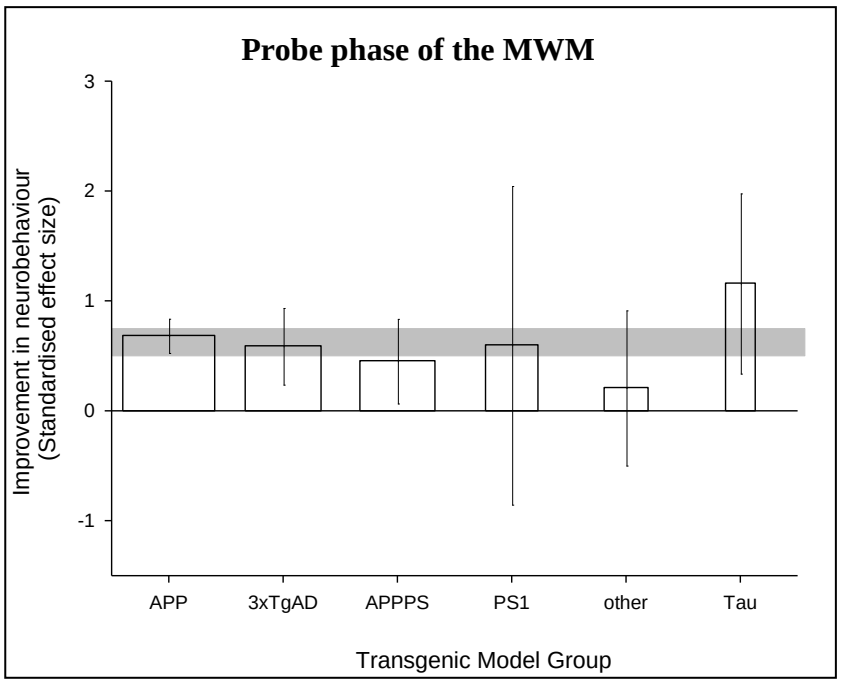


Figure 4.34: I stratified data from the probe phase of the Morris water maze (MWM) according to transgenic model group used. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

3xTgAD Effect size (95% CI) and N	APP Effect size (95% CI) and N	APPPS Effect size (95% CI) and N	PS1 Effect size (95% CI) and N	Other Effect size (95% CI) and N	Tau Effect size (95% CI) and N
0.6 (-0.85 to 2.05) **3**	0.69 (0.53 to 0.84) **70**	0.59 (0.24 to 0.94) **19**	0.46 (0.07 to 0.84) **18**	0.21 (-0.49 to 0.92) **2**	1.16 (0.34 to 1.98) **1**

Table 4.31: Estimates of efficacy in the probe phase of the MWM according to the transgenic mouse model group used. Estimates are given in Standardised mean difference estimates (SMD), brackets represent 95% confidence limits of this estimate and N represents number of experiments.

4.8.2 Stratified probe phase analyses

Experiments in the MWM varied in terms of the size of the pool, temperature of water used and the total number of trials. I performed stratified analyses on each of these to gain estimates of effect size for each quartile. I stratified results from the probe phase of the MWM by pool size where estimates of effect were relatively similar and this did not account for a significant proportion of the observed heterogeneity (96 experiments χ^2=2.05, Figure 4.35a). Where temperature of the MWM pool was stated (76 experiments) I found that the higher the temperature of the water used, the lower the estimate of efficacy (χ^2=36.3, p<0.02, Figure 4.35b). I stratified experiments by the total number of trials wherever stated (91 experiments). While, this accounted for a significant proportion of observed heterogeneity estimates of efficacy did not suggest a particular relationship (χ^2=21.96, p<0.02, 91 experiments, Figure 4.35c).

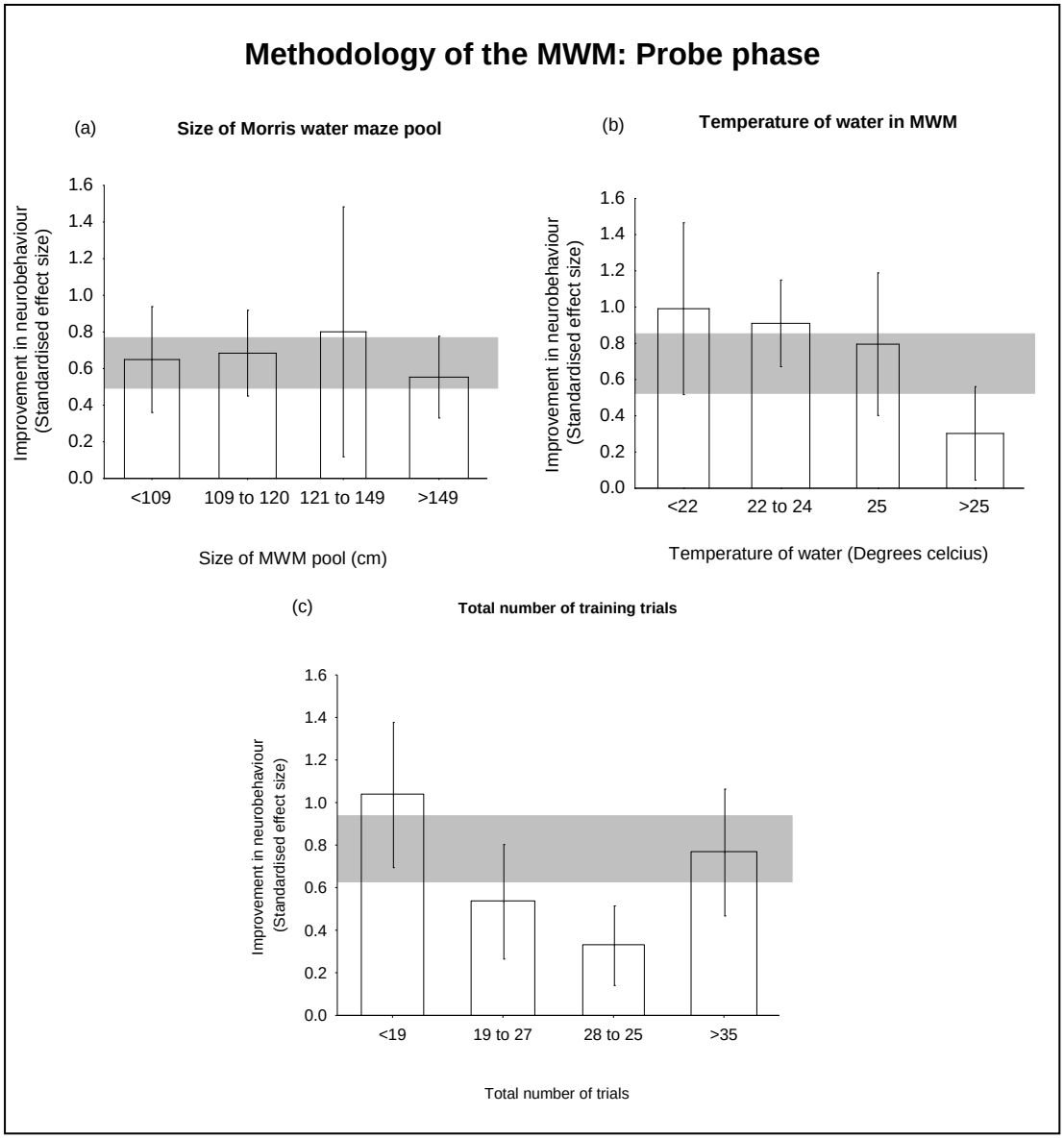


Figure 4.35: I stratified data from the probe phase of the Morris water maze (MWM) according to the size of the pool used (a), temperature of water (b) and total number of training trials (c). Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.8.3 Summary of probe phase of the Morris water maze

Overall, interventions successfully improved outcomes from the probe phase of the MWM and I did not observe differences in estimates according to different transgenic mouse model groups. For stratified analyses, smaller estimates of efficacy were with higher water temperatures and while stratifying by the total number of training trials accounted for a significant proportion of the observed heterogeneity, relationships were difficult to define.

4.9 Fear conditioning

Overall, data from 678 animals suggested that interventions improved fear conditioning outcomes by 0.70 SD (0.51 to 0.89, 45 comparisons). I identified that cued assessment of behaviour was associated with smaller effect sizes than contextual assessment (Table 4.32 and for further details see Chapter 3) and stratification accounted for a significant proportion of the observed heterogeneity (χ^2=8.79).

	Cued assessment	Contextual assessment	Summary estimate
Effect size 95& CI **n**	0.30 (0.01 to 0.60) **15**	0.81 (0.57 to 1.05) **45**	0.69 (0.5 to 0.89) **60**

Table 4.32: Estimates of standardised effect size according to whether the fear conditioning paradigm was used in the cued or contextual set up. End column indicates combined estimates Brackets provide 95 percent confidence limits and lower number indicates the number of experiments *as different outcomes can be represented in the same cohort of animals some are represented more than once.

I explored fear conditioning data further to identify whether I could examine potential relationships . For the 15 experiments which examined both cued and contextual memory (Table 4.33) I could use meta-regression analysis to explore relationships.

	Cued Effect size (95% CI) and N	Contextual Effect size (95% CI) and N	Combined Effect size (95% CI) and N
Cued only	No data		No data
Contextual only		0.79 (0.57 to 1.01) **30**	0.79 (0.57 to 1.01) **30**
Cued and contextual	0.30 (0.01 to 0.6) **15**	0.79 (0.17 to 1.42) **15**	0.56 (0.21 to 0.91) **15**
	Summary estimate	Summary estimate	Global estimate
	0.30 (0.01 to 0.6) **15**	0.81 (0.57 to 1.05) **45**	0.7 (0.51 to 0.89) **45**

Table 4.33: Estimates of effect size for fear conditioning and more specifically the cued and contextual learning tasks. For each, the standardised effect size is given with 95% confidence limits and the number of experiments.

4.9.1 Fear conditioning transgenic model groups

I stratified fear conditioning outcomes according to the transgenic model group used and found that this did not account for a significant proportion of the observed heterogeneity (χ^2=3.04, Figure 4.36). For informative purposes only I also describe transgenic model group estimates of efficacy within the cued and contextual constructs (Table 4.34).

Transgenic model Group	Cued Effect size (95% CI) and N	Contextual Effect size (95% CI) and N	Combined Effect size and N (95% CI) and N
APP	0.35 (0 to 0.7) **13**	0.84 (0.47 to 1.21) **29**	0.73 (0.45 to 1.02) **29**
APPPS	0.19 (-0.38 to 0.75) **2**	0.81 (0.52 to 1.1) **9**	0.68 (0.43 to 0.94) **9**
3xTgAD	**No data**	0.46 (-0.18 to 1.1) **6**	0.46 (-0.18 to 1.1) **6**
Tau	**No data**	1.58 (0.29 to 2.88) **1**	1.58 (0.29 to 2.88) **1**
PS1	**No data**	**No data**	**No data**
Other	**No data**	**No data**	**No data**
	Summary estimate	**Summary estimate**	**Global estimate**
	0.3 (0.01 to 0.6) 15	0.81 (0.57 to 1.05) 45	0.70 (0.51 to 0.89) 45

Table 4.34: Estimates of effect size by transgenic model group for fear conditioning and more specifically the cued and contextual learning tasks. For each, the standardised effect size is given with 95% confidence limits and the number of experiments.

4.9.2 Relationships between fear conditioning outcomes

For the 15 experiments where both contextual and cued fear conditioning were assessed I performed meta-regression to identify potential relationships. However the value of tau (study heterogeneity) was insufficient for an R^2 value to be calculated.

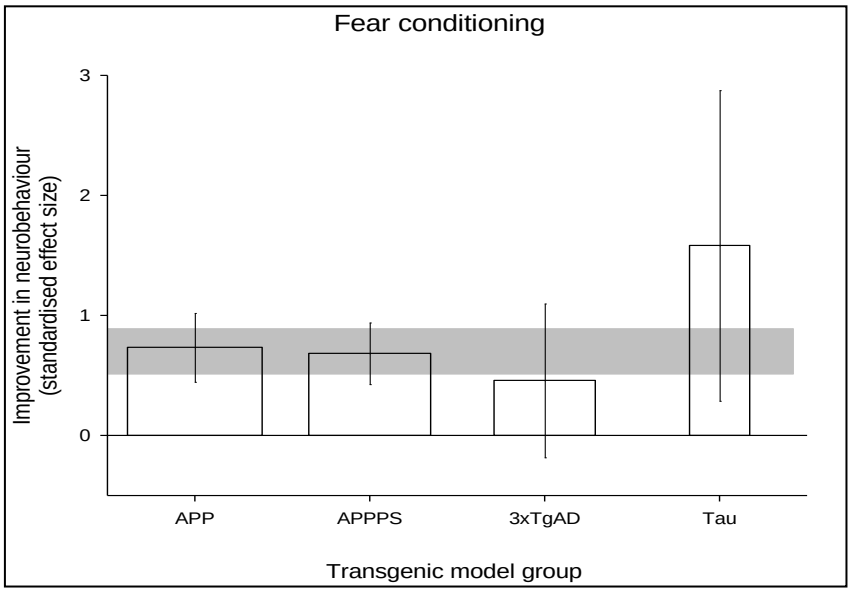


Figure 4.36 (previous): I stratified data from the fear conditioning paradigm according to the transgenic model group used which did not account for a significant proportion of heterogeneity. Error bars represent 95% confidence intervals (CI), grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.9.3 Summary of fear conditioning outcomes

Overall, interventions successfully improved outcomes in the fear conditioning paradigm, and also more specifically when examining the cued and contextual learning in isolation. Stratifying data according to the transgenic model group used identified that estimates were relatively similar and this did not account for a significant proportion of the observed heterogeneity.

4.10 Radial arm water maze

Overall, interventions improved outcomes in the radial arm water maze by 0.86 SD (0.61 to 1.10, 41 comparisons n=678 animals, $\chi^2 = 98.66$). I explored the sensitivity of different methodological set ups and while estimates of efficacy differed, this did not account for a significant proportion of the observed heterogeneity ($\chi^2 = 5.88$, $p<0.05$, Table 4.35). As each methodology could only be used for a single experiment I could not investigate relationships between the different methodologies used.

	Single platform assessment	Baited arms assessment	Unclear	Summary estimate
Effect size (95% CI) N	1.01 (0.7 to 1.32) **29**	0.59 (0.13 to 1.04) **10**	0.68 (-0.4 to 1.75) **2**	0.86 (0.61 to 1.1) **41**

Table 4.35: Estimates of standardised effect size according to how the radial arm maze paradigm was used. End column indicates the overall estimate Brackets provide 95 percent confidence limits and lower number indicates the number of experiments.

4.10.1 RAWM transgenic model group estimates

I stratified RAWM outcomes according to the transgenic model group used where this did not account for a significant proportion of the observed heterogeneity (χ^2=2.68, Figure 4.37). For informative purposes only I also describe transgenic model group estimates of efficacy within the cued and contextual constructs (Table 4.36).

Transgenic model Group	Single platform Effect size (95% CI) and N	Baited arms Effect size (95% CI) and N	Unclear Effect size (95% CI) and N	Combined Effect size (95% CI) and N
APP	1 (0.6 to 1.4) **11**	0.72 (-0.04 to 1.48) **7**	No data	0.91 (0.49 to 1.33) **18**
APPPS	0.98 (0.54 to 1.41) **17**	0.37 (0.07 to 0.67) **3**	0.68 (-0.4 to 1.75) **2**	0.8 (0.48 to 1.11) **22**
3xTgAD	No data	No data	No data	No data
Tau	No data	No data	No data	**No data**
PS1	1.41 (0.28 to 2.55) **1**	No data	No data	1.41 (0.28 to 2.55) **1**
Other	No data	No data	No data	**No data**
	Summary estimate	**Summary estimate**	**Summary estimate**	**Global estimate**
	1.01 (0.7 to 1.32) **29**	0.48 (-0.04 to 1.01) **10**	0.68 (-0.4 to 1.75) **2**	0.86 (0.61 to 1.1) **41**

Table 4.36: Estimates of efficacy according to the transgenic mouse model group used. Estimates are given in Standardised mean difference estimates (SD), brackets represent 95% confidence limits of this estimate and N represents number of experiments.

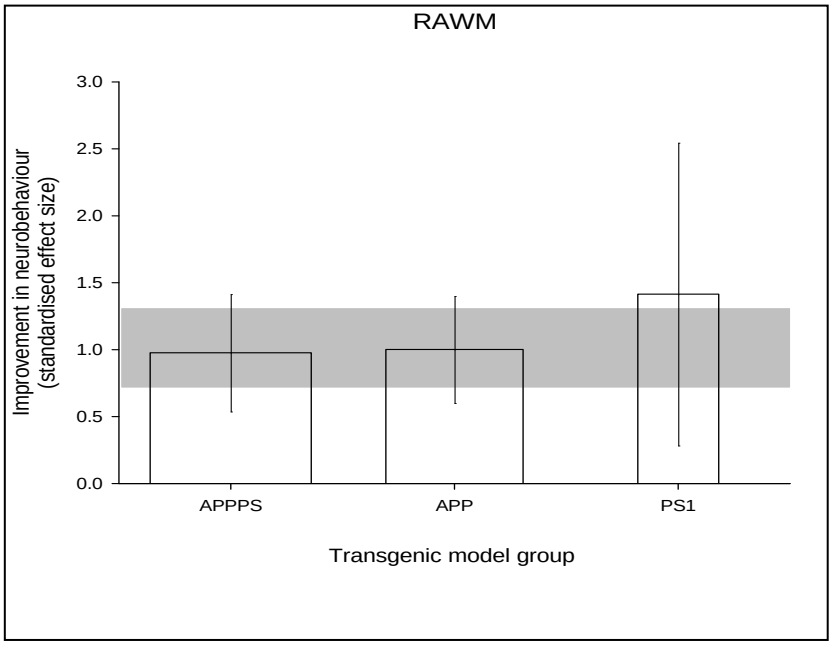


Figure 4.37 I stratified data from the radial arm water maze (RAWM) according to the transgenic model group used but this did not account for a significant proportion of the observed heterogeneity. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.10.2 Summary of RAWM

Overall, interventions successfully improved outcomes within the RAWM. Methodologies differed in overall estimates of effect size and I identified that the transgenic model group accounted for a significant proportion of the observed heterogeneity.

4.11 Novel object recognition task

Overall interventions improved outcomes by 0.95 SD (95% CI 0.63 to 1.27, N=460 animals). I explored the sensitivity of different methodological set ups but did not identify potential areas for stratification. Thus, I first stratified data according to the transgenic model group used.

4.11.1 NORT and transgenic model groups

Estimates of efficacy across different transgenic model groups were notably different and stratification accounted for a significant proportion of the observed heterogeneity (Table 4.37, Figure 4.38, χ^2=13.33, p<0.05) however interpretation was difficult due to large confidence limits which frequently overlapped and few data being present.

APP Effect size (95% CI) and N	APPPS Effect size (95% CI) and N	3xTgAD Effect size (95% CI) and N	Tau Effect size (95% CI) and N	Other Effect size (95% CI) and N	Combined Effect size (95% CI) and N
1.23 (0.77 to 1.68) **15**	0.82 (0 to 1.63) **5**	0.29 (-0.7 to 1.28) **1**	-0.22 (-1.02 to 0.59) **1**	0.63 (0.19 to 1.07) **3**	0.95 (0.63 to 1.27) **25**

Table 4.37: Estimates of efficacy according to the transgenic mouse model group used. Estimates are given in Standardised mean difference estimates), brackets represent 95% confidence limits of this estimate and N represents number of experiments.

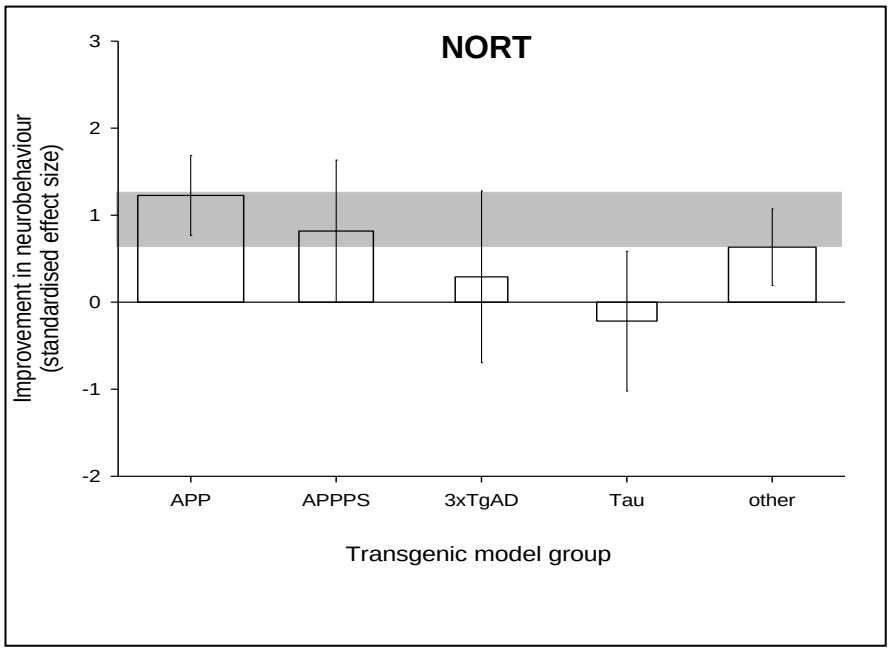


Figure 4.38: I stratified data from the novel object recognition task (NORT) according to the transgenic model group used. Error bars represent 95% confidence intervals (CI) and grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.11.2 Relationships within NORT outcomes

While I explored the NORT dataset for potential ways to stratify data, this was not possible within the dataset extracted.

4.11.3 NORT summary

Compared to other neurobehavioural tasks data were few for the novel object recognition task (25 experiments). Nevertheless, I identified that interventions successfully improved NORT outcomes, and stratifying by the transgenic model used accounted for a significant proportion of the observed heterogeneity.

4.12 T maze & Y maze

Due to similarities between the T and Y maze I merged the two datasets together in order to increase overall statistical power. Across the two paradigms I estimated that interventions improved outcomes by 0.46 SD (0.21 to 0.71, 28 experiments). I first derived estimates of efficacy and assessed heterogeneity by stratifying data according to each paradigm. I identified broadly similar estimates between the T and Y maze with improvements of 0.56 SD (0.17 to 0.95) and 0.39 SD (0.06 to 0.72) respectively (Table 4.38) and this did not account for a significant proportion of the observed heterogeneity (χ^2=1.33).

	T maze assessment	Y maze assessment	Overall estimate*
Effect size 95 CI **n**	0.56 (0.17 to 0.95) **11**	0.39 (0.06 to 0.72) **17**	0.46 (0.21 to 0.71) **28**

Table 4.38: Estimates of standardised effect size were assessed according to whether mice were tested in the T-maze or Y-maze, 95% confidence limits (95% CI) and number of experiments. End column indicates the overall estimate *as no experiments examined both measures animals are not represented more than once.

I explored data further and identified that no mice were assessed in both the T maze and Y maze and thus I could not investigate potential relationships between the two paradigms (Table 4.39).

	T maze Effect size (95% CI) and N	Y maze Effect size (95% CI) and N	Combined Effect size (95% CI) and N
T maze only	0.56 (0.17 to 0.95) **11**		0.56 (0.17 to 0.95) **11**
Y maze only		0.39 (0.06 to 0.72) **17**	0.39 (0.06 to 0.72) **17**
Y and T maze	**No data**	**No data**	**No data**
	Summary estimate	**Summary estimate**	**Global estimate**
	0.56 (0.17 to 0.95) **11**	0.39 (0.06 to 0.72) **17**	0.46 (0.21 to 0.71) **28**

Table 4.39: Estimates of effect size for the T and Y maze as individual paradigms and a combined single outcome measure. For each, the standardised effect size is given with 95% confidence limits and the number of experiments.

4.12.1 Transgenic model groups and T and Y maze

I stratified data according the transgenic mouse model used and found higher estimates of efficacy with the APP transgenic model group 0.89 SD (0.25 to 1.53) compared to the APPPS transgenic group 0.20 SD (-0.11 to 0.51 (or the 3xTgAD transgenic group 0.69 SD (0.20 to 1.18) where this account for a significant proportion of the observed heterogeneity (χ^2=7.91, df=2,p<0.05). For informative purposes I also describe transgenic model group specific estimates of efficacy for the T and Y maze individually (Table 4.40).

Transgenic model Group	T maze Effect size (95% CI) and N	Y maze Effect size (95% CI) and N	Combined Effect size and N (95% CI) and N
APP	0.73 (-0.51 to 1.97) **2**	1.02 (0.21 to 1.82) **4**	0.89 (0.25 to 1.53) **6**
APPPS	0.5 (-0.19 to 1.2) **5**	0.05 (-0.26 to 0.36) **10**	0.20 (-0.11 to 0.51) **15**
3xTgAD	0.55 (0 to 1.09) **4**	0.91 (-0.1 to 1.92) **3**	0.69 (0.2 to 1.18) **7**
Tau	**No data**	**No data**	**No data**
PS1	**No data**	**No data**	**No data**
Other	**No data**	**No data**	**No data**
	Summary estimate	**Summary estimate**	**Global estimate**
	0.56 (0.17 to 0.95) **11**	0.39 (0.06 to 0.72) **17**	0.46 (0.21 to 0.71) **28**

Table 4.40: Estimates of effect size by transgenic model group for the T and Y maze individually, and combined. For each, the standardised effect size is given with 95% confidence limits and the number of experiments.

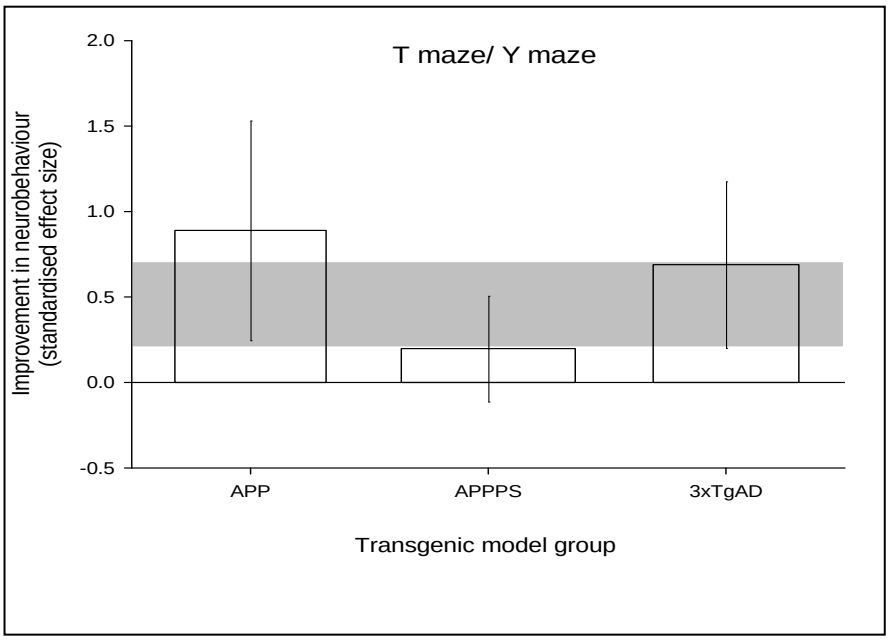


Figure 4.39: I stratified data from the T and Y maze by the transgenic model group used but this did not account for significant proportion of the observed heterogeneity. Error bars represent 95% confidence intervals (CI); grey bar represents 95% CI of global estimate, bar width represents the log of the number of animals.

4.12.2 Summary of Y and T maze

Overall, interventions successfully improved outcomes both within the Y and T maze individually and collectively. Our estimates of efficacy did not suggest it might be inappropriate to combine the two datasets. Although I observed differences in estimates of efficacy across different transgenic mouse models this was not reflected in terms of heterogeneity.

4.13 Summary of neurobehavioral outcomes and potential relationships

Understanding potential relationships between different behavioural paradigms is likely to provide insights which could assist preclinical trial design. Therefore, I used the six principle behavioural paradigms to investigate potential relationships between different behavioural tests. Despite a potential 15 comparisons I could only identify sufficient data to inspect the relationship between the acquisition and probe phase of the MWM (>10 outcomes, for summary see Table 4.41)

Therefore, I performed meta-regression in order to identify whether variance in the acquisition phase of the MWM could be a reliable predictor for variance in the probe phase. Using data from 78 experiments, performance across the acquisition phase could explain 44% of the variation in the probe phase (Figure 4.20a).

I explored this dataset further to identify whether different stages of the acquisition phase correlated better with the probe phase than others. Therefore I calculated individual estimates of effect and segregated data into: (i) first, (ii) between first and last, and (iii) last time points. Meta-regression identified that the proportion of variation in the probe which could be explained by acquisition phase variation sequentially increased with a respective R^2 of (i)13%, (ii) 57% and 59% (See Table 4.42 and Figure 4.20b-d).

Table 4.41 (next page): Estimates of standardised effect size according to where single cohort was used to assess more than one behavioural outcome measures. Columns represent the acquisition and probe phase of the Morris water maze (MWM), Radial arm water maze (RAWM), Fear conditioning, Novel object recognition task (NORT) and Y/T-maze. End column indicates combined estimates. Brackets give 95 percent confidence limits and lower number indicates the number of experiments. (N.B. some experiments may be represented more than once).

Acquisition ES (95% CI) and N	Probe phase ES (95% CI) and N	RAWM ES (95% CI) and N	Fear ES (95% CI) and N	NORT ES (95% CI) and N	T/Y-maze ES (95% CI) and N	Combined ES (95% CI) and N
0.38 (0.23 to 0.53) **50**						0.38 (0.23 to 0.52) **50**
	0.54 (0.3 to 0.78) **24**					0.54 (0.3 to 0.78) **24**
		0.88 (0.49 to 1.26) **24**				0.88 (0.51 to 1.26) **24**
			0.65 (0.38 to 0.93) **33**			0.7 (0.45 to 0.95) **33**
				0.74 (0.3 to 1.18) **16**		0.84 (0.47 to 1.2) **16**
					0.34 (0.05 to 0.64) **12**	0.34 (0.05 to 0.64) **12**
0.55 (0.45 to 0.66) **78**	0.70 (0.53 to 0.87) **78**					0.65 (0.52 to 0.77) **78**
0.60 (0.27 to 0.94) **8**		0.78 (0.41 to 1.14) **8**				0.73 (0.42 to 1.04) **8**
0.46 (0.07 to 0.86) **5**			0.69 (0.15 to 1.23) **5**			0.57 (0.21 to 0.93) **5**
0.46 (-0.01 to 0.93) **2**				1.78 (-1.18 to 4.75) **2**		0.68 (0.02 to 1.35) **2**
0.39 (0.11 to 0.66) **9**					0.30 (-0.17 to 0.77) **9**	0.32 (0.01 to 0.63) **9**
	0.38 (-0.07 to 0.84) **10**	0.78 (0.45 to 1.11) **10**				0.58 (0.22 to 0.93) **10**
	0.94 (0.52 to 1.35) **6**		0.69 (0.29 to 1.1) **6**			0.82 (0.53 to 1.12) **6**
	0.71 (0.38 to 1.04) **8**			1.11 (0.43 to 1.79) **8**		0.86 (0.56 to 1.15) **8**
	0.59 (-0.03 to 1.2) **9**				0.34 (-0.16 to 0.84) **9**	0.45 (-0.03 to **9**
		1.22 (0.19 to 2.24) **3**	0.72 (0.36 to 1.08) **3**			0.92 (0.39 to 1.45) **4**
		No data		**No data**		**No data**
		0.46 (0.19 to 0.73) **6**			0.33 (-0.38 to 1.03) **6**	0.43 (0.2 to 0.65) **6**
			1.12 (0.6 to 1.63) **2**	1.78 (-1.18 to **2**		1.14 (0.24 to 2.03) **2**
			0.67 (-0.36 to 1.7) **3**		0.76 (0.16 to 1.37) **3**	0.74 (0.02 to 1.47) **3**
				1.07 (-0.33 to **1**	1.44 (-0.06 to 2.95) **1**	1.25 (0.22 to 2.27) **1**
Summary estimate	**Summary estimate**	**Summary estimate**	**Summary estimate**	**Summary estimate**	**Summary estimate**	**Global estimate**
0.49 (0.41 to 0.58) **130**	0.63 (0.5 to 0.76) **113**	0.86 (0.61 to 1.1) **41**	0.7 (0.51 to 0.89) **45**	0.95 (0.63 to 1.27) **25**	0.46 (0.21 to 0.71) **28**	0.61 (0.54 to 0.69) **259**

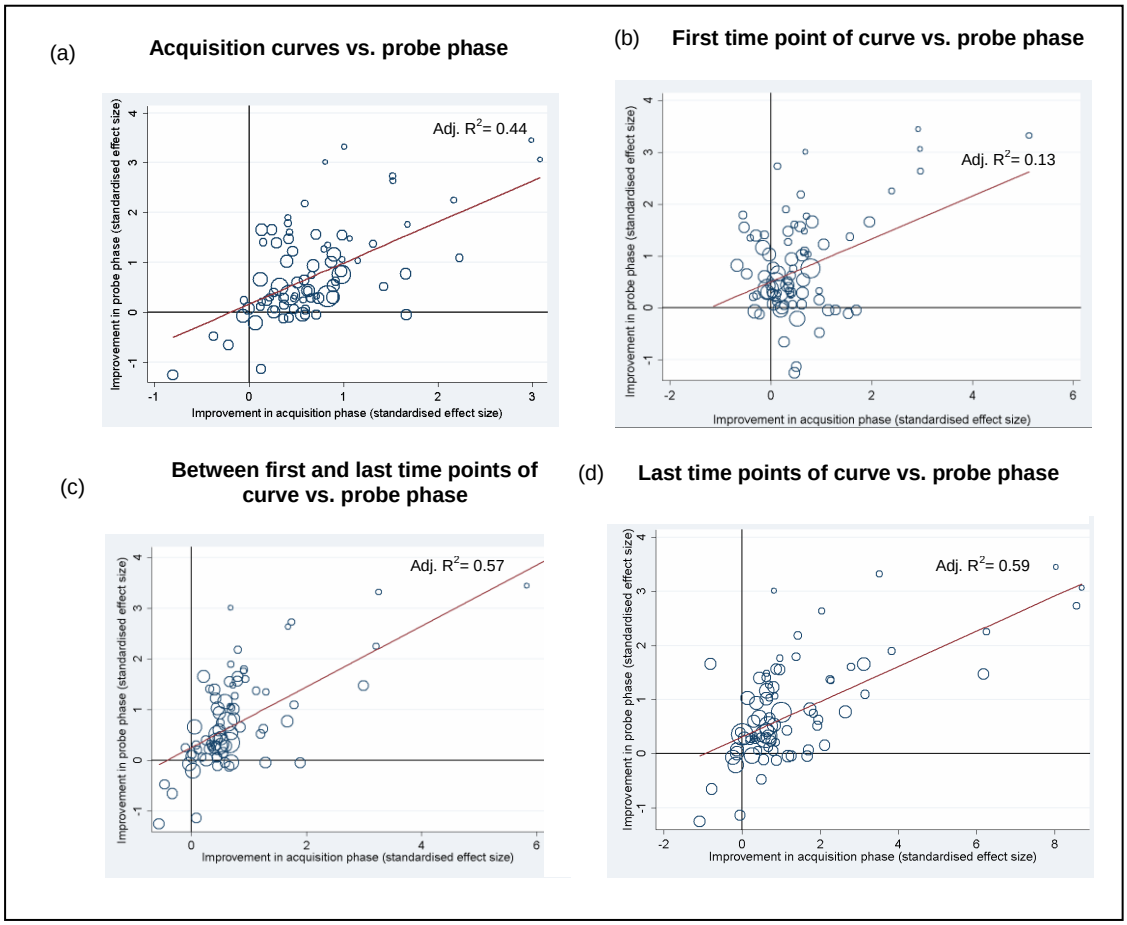


Figure 4.40: Meta-regression comparing probe phase with acquisition curves, first and last time point of acquisition curve and sections in between. For each comparison Adjusted R^2 (Adj. R^2) is given. Symbol size represents the inverse of variance,

	Co-efficient (SMD ES)	Standard error	τ	P>|t| **where α=0.01**	Lower 95% CI	Upper 95 CI%	N	Adj. R^2
Acquisition curve vs. probe phase	0.826	0.14	5.89	0	0.547	1.105	**78**	**0.44**
First time point of acquisition vs. probe phase	**0.414**	**0.114**	**3.62**	**0.001**	**0.186**	**0.642**	**78**	**0.13**
Between first and last time point of acquisition vs. probe phase	0.601	0.087	6.94	0	0.428	0.773	**78**	**0.57**
last time point of acquisition vs. probe phase between	0.325	0.047	6.95	0	0.232	0.418	**78**	**0.59**

Table 4.42: Meta-regression comparing probe phase with acquisition curves, first and last time point of acquisition curve and sections in-between. For each comparison co-efficient is given, standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2).

4.14 Summarising pathological and neurobehavioural outcomes

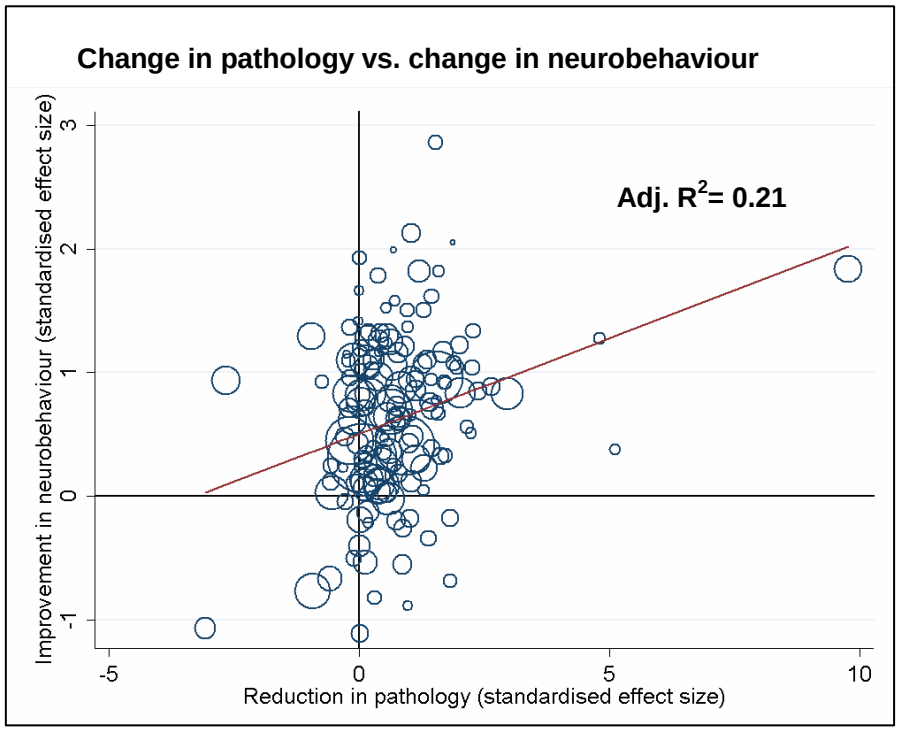
The overall estimates of efficacy for structural and behavioural outcomes were 0.78 SD (0.71 to 0.85, 725 experiments) and 0.61 SD (0.54 to 0.69, 259 experiments). I was interested whether changes in structural pathology could explain changes in neurobehavioural function and identified that 146 experiment measured both of these (see Table 4.43 for summary estimates).

	Structural outcome Effect size (95% CI) and N	Functional outcome Effect size (95% CI) and N
Structural outcomes only	0.84 (0.75 to 0.92) **579**	
Functional outcomes only		0.61 (0.50 to 0.72) **113**
Both structural and functional outcomes	0.63 (0.51 to 0.75) **146**	0.61 (0.51 to 0.71) **146**
	Summary estimate	**Summary estimate**
	0.78 (0.71 to 0.85) **725**	0.61 (0.54 to 0.69) **259**

Table 4.43: Estimates of effect size for changes in pathological structural outcomes and neurobehavioural function. For each, the standardised effect size is given with 95% confidence limits and the number of experiments.

4.14.1 Overall relationship between pathology and neurobehaviour

Therefore I took forward estimates of effect from 147 experiments to identify whether structural changes could explain and functional changes. Our meta-regression identified that 20.6% of the overall variation in behaviour could be explained by variation of pathology (Figure 4.44, Table 4.39).



	Co-efficient (SMD Effect size)	Standard Error	t	P>|t| where α=0.05	Lower 95% CI	Upper 95% CI	N	Adj. R^2
All pathology vs. all neurobehaviour	0.155	0.039	3.93	0	0.077	0.232	146	0.21

Figure 4.41 (upper) and Table 4.44 (lower): I performed meta-regression in order to understand whether changes in pathological outcomes could explain changes in neurobehavioural outcomes. Symbol size represents the inverse of variance, For comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

4.14.2 Relationships between specific pathologies and neurobehaviour

To identify whether individual pathologies might have greater or lesser impacts on neurobehaviour I explored the spread of the data (Table 4.40). I identified that sufficient data were present to investigate each of the individual pathologies in isolation (where I used an α=0.009, Table 4.45 for all analyses)

	Plaque burden	Amyloid beta 40	Amyloid beta 42	Tau	Cellular infiltrates	Neurodegeneration
Neurobehavioral outcomes	100*	88*	94*	17*	24*	20*

Table 4.45: I explored cohort datasets to identify where individual pathological experiments were performed alongside neurobehavioural assessment *sufficient data were present to allow analyses across all pathologies.

For meta-regression analyses (see Table 4.46) 100 experiments suggested that changes in plaque pathology could explain 31% of changes in neurobehaviour (Figure 4.42a). 89 experiments suggested that amyloid beta 40 could explain 12% of the variation in neurobehavioural outcomes but this did not prove statistically significant (Figure 4.42b) whereas changes in amyloid beta 42 explained 22% of neurobehavioural changes (Figure 42c, $p<0.009$).

For the 17 tau experiments where neurobehavioural outcomes were measured I did not identify a correlation between changes (Figure 4.42d). Similarly changes in cellular infiltrates [24 experiments] did not explain changes in neurobehaviour (Figure 4.42e). For outcomes regarding neurodegeneration however, 20 experiments suggested that changes in pathology could explain 71.93% of the changes in neurobehaviour (Figure 4.42f)

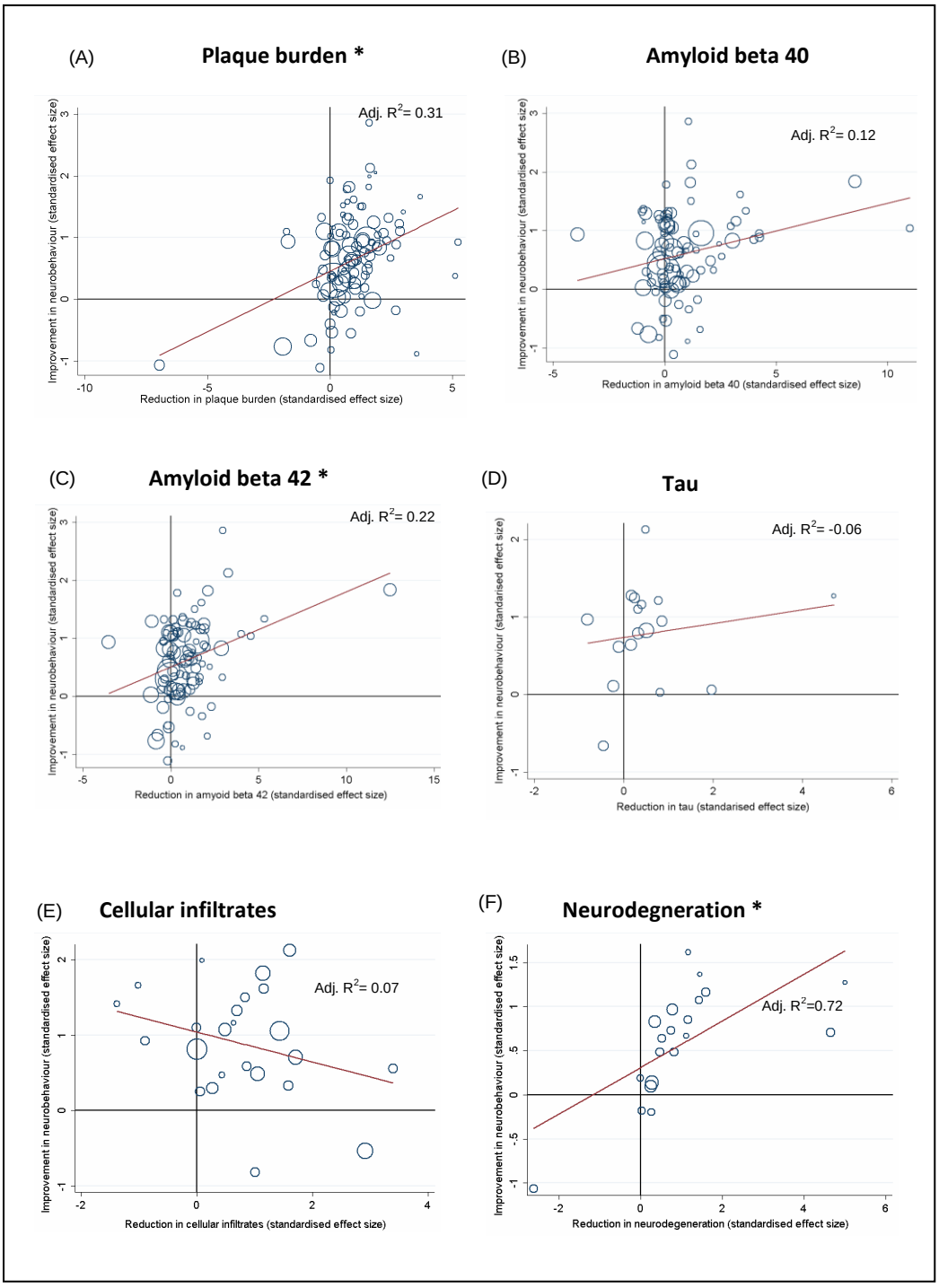


Figure 4.42 (previous page): I performed meta-regression in order to understand whether changes in pathological outcomes could explain changes in neurobehavioural outcomes. For each comparison adjusted R^2 (Adj. R^2) is given. Symbol size represents the inverse of variance.

	Co-efficient (ES)	Standard Error	t	P>|t| where α=0.009	Lower 95% CI	Upper 95% CI	N	Adj. R^2
Plaque burden vs. NBS	0.196	0.047	4.19	0	0.103	0.289	100	0.31
Aβ 40 vs. NBS	0.094	0.038	2.5	0.014	0.019	0.169	88	0.12
Aβ 42 vs. NBS	0.13	0.035	3.68	0	0.06	0.2	94	0.22
Tau vs. NBS	0.09	0.165	0.54	0.594	-0.261	0.441	17	-0.06
Cellular infiltrates vs. NBS	-0.2	0.151	-1.32	0.2	-0.513	0.114	24	0.07
Neurodegeneration vs. NBS	0.265	0.076	3.47	0.003	0.104	0.426	20	0.72

Table 4.46: I investigated potential relationships between each pathological outcome and neurobehaviour. For each comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

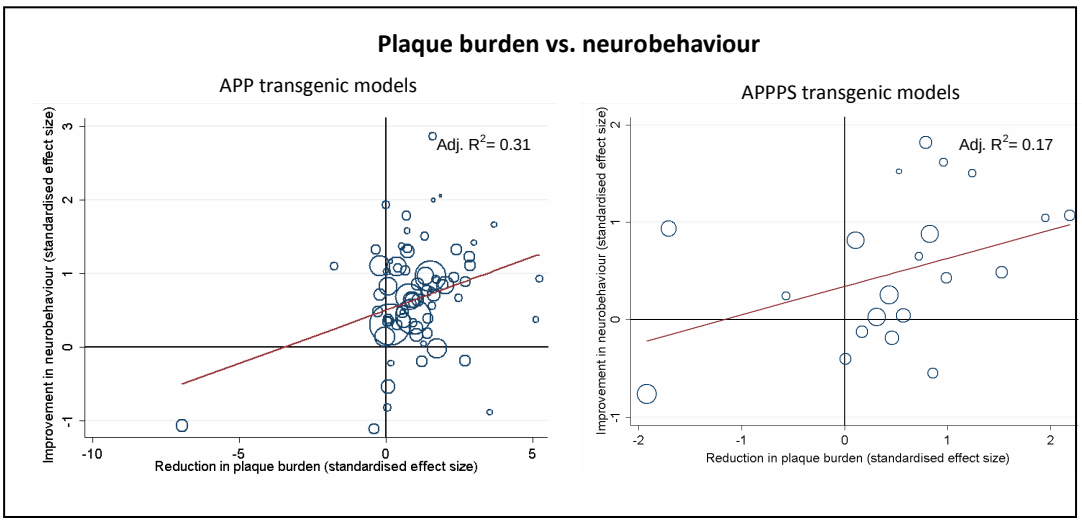
4.14.3 Relationships between pathologies and neurobehaviour by transgenic model group

Although I maximised statistical power by pooling all transgenic models in order to define relationships between pathological and neurobehavioural outcomes the approach does not consider differences in pathologies between the models. Therefore, I examined how much data were present within individual transgenic model groups for possible further analyses. I identified that there were sufficient data to analyses relationships between a number of transgenic model group pathologies and neurobehaviour shown in Table 4.47.

	Plaque burden	Amyloid beta 40	Amyloid beta 42	Tau	Cellular infiltrates	Neurodegeneration
APP	72*	57*	61*	2	15*	14*
APPPS	21*	21*	21*	1	8	5
3xTgAD	7	10*	10*	14*	1	0
Tau	0	0	1	0	0	1
PS1	0	0	0	0	0	0
Other	0	0	1	0	0	0
All Transgenic model groups	100*	88*	94*	17*	24*	20*

Table 4.47: Table describes number of individual experiments where pathological outcomes were examined alongside neurobehavioural outcomes,*sufficient data for analyses.

Therefore, I was able to examine the relationship between plaque burden and neurobehaviour for both the APP and APPPS transgenic model groups (Table 4.48). For APP transgenic models meta-regression suggested that 30.6% of the variation in neurobehaviour could be explained by variation in plaque burden (Figure 4.23a). However, where I examined APPPS mice I identified that reductions in plaque pathology could not explain improvements in neurobehaviour (Figure 4.23b)

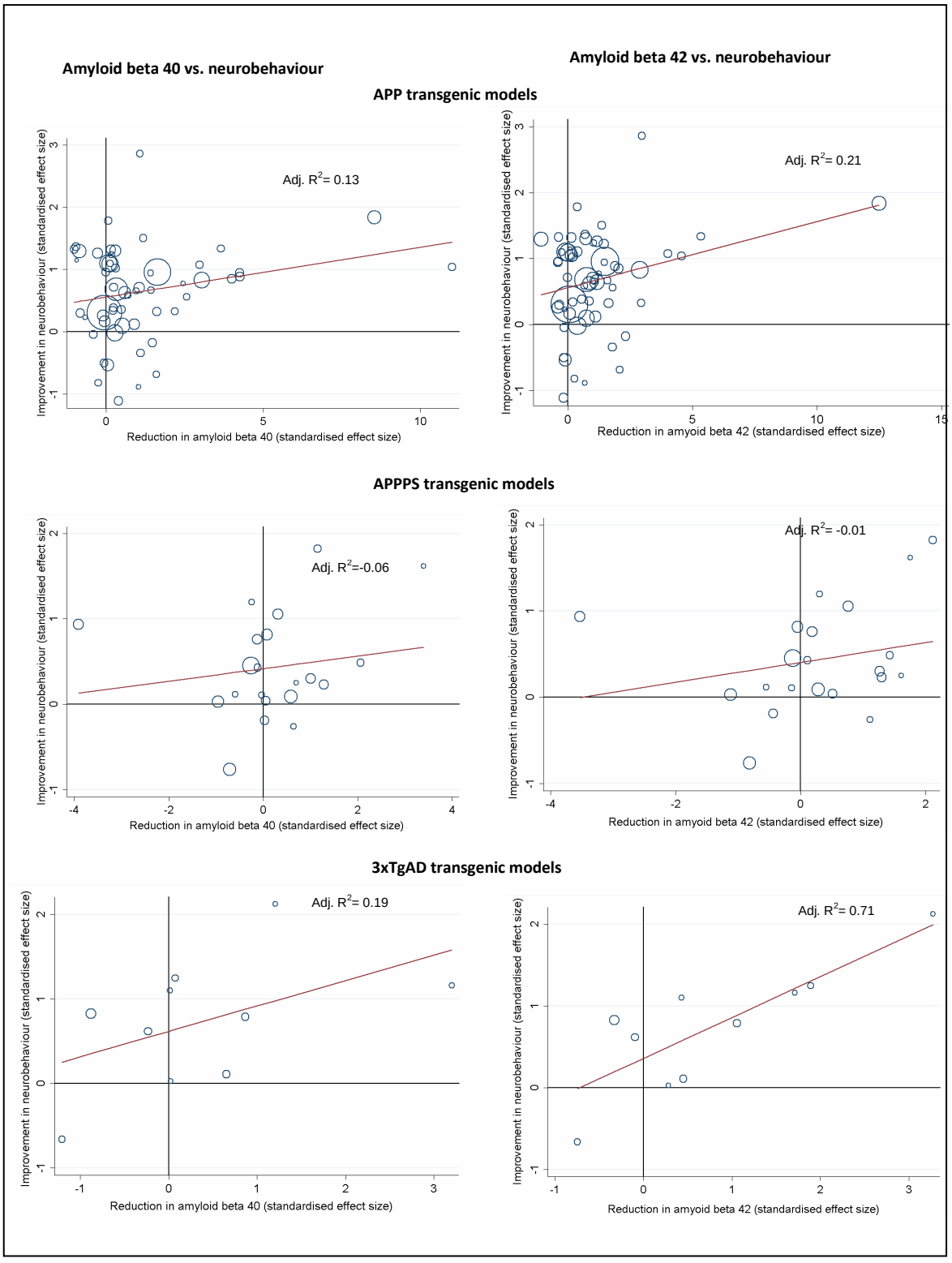


Transgenic group	Co-efficient (SMD ES)	Standard Error	t	P>|t| where α=0.03	Lower 95% CI	Upper 95% CI	N	Adj. R^2
APP	0.144	0.048	2.98	0.004	0.047	0.240	72	0.31
APPPS	0.290	0.149	1.95	0.066	-0.021	0.602	21	0.17

Figure 4.43 (upper) and Table 4.48 (lower): I assessed whether changes in plaque burden could explain changes in neurobehaviour within the APP and APPPS transgenic model groups. Symbol size represents the inverse of variance.
For each comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2).

For amyloid beta 40 I was able to perform meta-regression analyses on the APP, APPPS and 3xTgAD groups respectively (Table 4.49). Our meta-regression analyses suggested that 13% of the variation in pathology could explain variations in neurobehaviour (Figure 4.24a). I did not identify a statistically significant relationship between variation in amyloid beta 40 and neurobehaviour in APPPS models (Figure 4.24b) or within 3xTgAD models (Figure 4.24c).

Figure 4.44 (next page): I assessed whether changes in amyloid beta 40 (a,b,c) and amyloid beta 42 (d,e,f) could explain changes in neurobehaviour within the APP APPPS and 3xTgAD. transgenic model groups. For each comparison Adjusted R^2 (Adj. R^2) is given. Symbol size represents the inverse of variance.


Amyloid beta 40 vs. neurobehaviour
Amyloid beta 42 vs. neurobehaviour
APP transgenic models
Adj. R²= 0.13
Adj. R²= 0.21
Improvement in neurobehaviour (standardised effect size)
Reduction in amyloid beta 40 (standardised effect size)
Reduction in amyoid beta 42 (standardised effect size)
APPPS transgenic models
Adj. R²=-0.06
Adj. R²= -0.01
3xTgAD transgenic models
Adj. R²= 0.19
Adj. R²= 0.71

For amyloid beta 42 I was able to perform meta-regression analyses on the APP, APPPS and 3xTgAD groups respectively (Table 4.49). 62 APP experiments suggested that changes in amyloid beta 42 could explain 21% of changes in neurobehaviour (Figure 4.23d). I did not identify a statistically significant relationship within the APPPS transgenic group (Figure 4.23e). Where I examined 10 3xTgAD experiments I identified a strong correlation between changes in amyloid beta 42 and neurobehaviour (R^2 = 71 %).

Transgenic model group	Co-efficient (SMD Effect size)	Standard Error	t	P>|t| where α=0.02	Lower 95% CI	Upper 95% CI	N	Adj. R^2
Amyloid beta 40								
APP	0.08	0.043	1.87	0.067	-0.006	0.166	57	0.13
APPPS	0.073	0.105	0.7	0.493	-0.146	0.293	21	-0.06
3xTgAD	0.302	0.191	1.59	0.151	-0.137	0.742	10	0.19
Amyloid beta 42								
APP	0.1	0.039	2.56	0.013	0.022	0.179	61	0.21
APPPS	0.115	0.11	1.05	0.307	-0.114	0.345	21	-0.01
3xTgAD	0.5	0.144	3.48	0.008	0.169	0.831	10	0.71

Table 4.49: I assessed whether changes in amyloid beta 40 and amyloid beta 42 could explain changes in neurobehaviour within the APP, APPPS and 3xTgAD transgenic model groups. For each comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

For tau neurofibrillary tangles, I assessed whether changes in 14 tau experiments could explain changes in neurobehaviour within the 3xTgAD mouse model. However, I did not identify a significant correlation between tau and neurobehaviour (Table 4.50, Figure 4.25).

For cellular infiltrates 15 APP experiments suggested a potential correlation between changes in cellular infiltrates and neurobehaviour however this did not reach statistical significance (Table 4.50, Figure 4.25). Finally, 14 APP experiments suggested that changes in neurodegeneration could explain 60% of changes in neurobehaviour (Table 4.50, Figure 4.25).

Transgenic model group	Co-efficient (SMD Effect size)	Standard Error	t	P>|t| where α=0.05	Lower 95% CI	Upper 95% CI	N	Adj. R^2
Tau								
3xTgAD	0.119	0.336	0.35	0.729	-0.612	0.85	14	-0.11
Cellular infiltrates								
APP	-0.325	0.134	-2.43	0.03	-0.614	-0.037	15	0.67
Neurodegeneration								
APP	0.25	0.09	2.76	0.017	0.053	0.447	14	0.60

Table 4.50: I assessed relationships between pathological outcomes and neurobehaviour within specific transgenic model groups wherever sufficient data were present. Data included Tau outcomes within 3xTgAD mice, cellular infiltrates within APP mice, and neurodegeneration outcomes within APP mice. For each comparison co-efficient is given (in terms of standardise mean difference effect size [SMD ES], standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

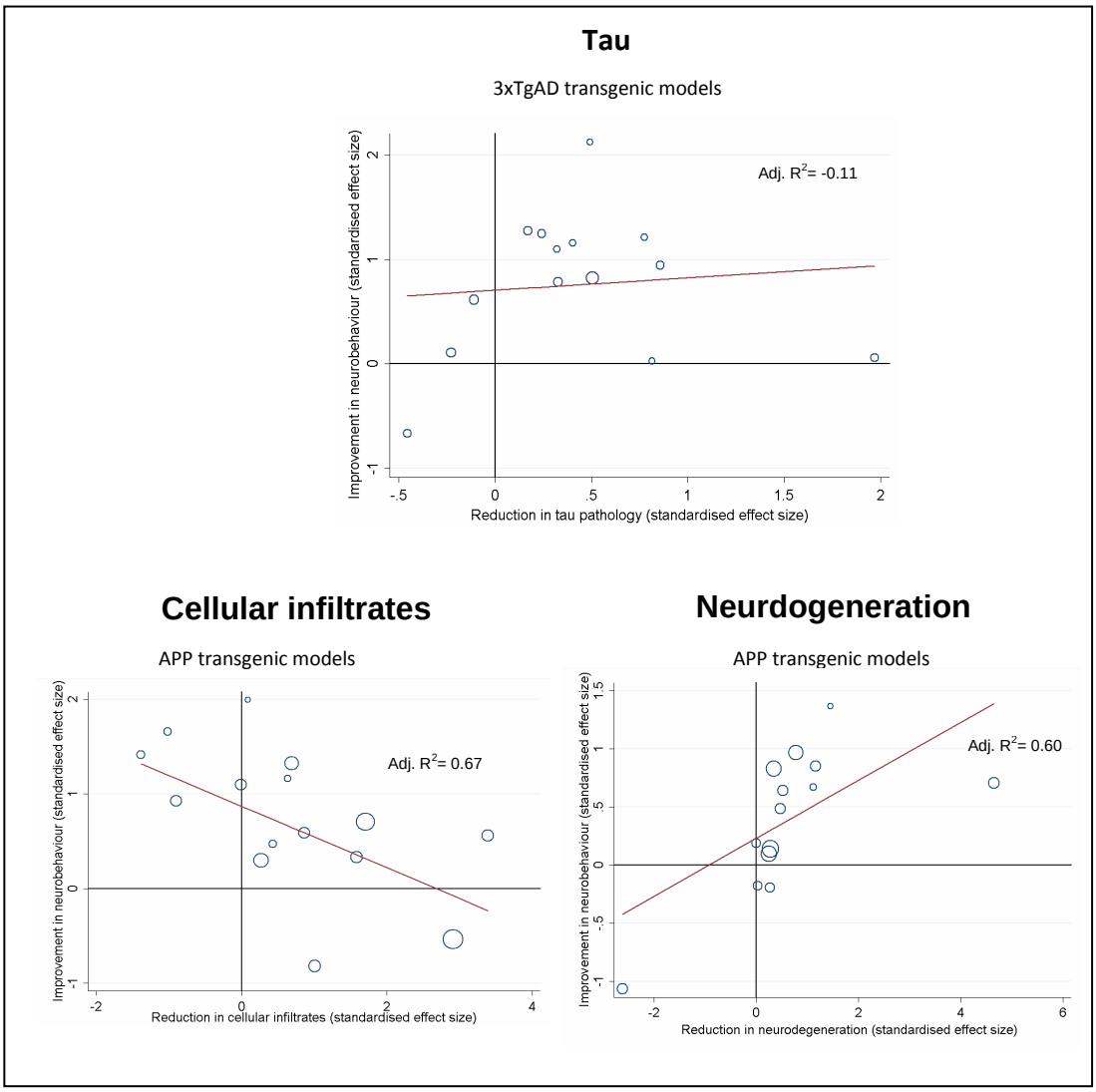


Figure 4.45: I assessed relationships between pathological outcomes and neurobehaviour within specific transgenic model groups wherever sufficient data were present. Data included Tau outcomes within 3xTgAD mice (a), cellular infiltrates within APP mice (b), and neurodegeneration outcomes within APP mice. (c) For each comparison Adjusted R^2 (Adj. R^2) is given. Symbol size represents the

4.15 Interpreting outcome measure analyses

4.15.1 Summary of findings

I identified a number of interesting relationships both within and between outcome measures. Changes in antibody stained plaque burden correlated well with both Thioflavin S and congo red stained plaques which is reassuring in terms of external validity. For measuring changes in amyloid species I noted a number of correlations, in particular that changes in amyloid beta 40 reflected changes amyloid beta 42. For outcomes regarding tau, I did not identify a correlation between improvements in the extent of phosphorylated tau and reductions and overall tau which was somewhat surprising. While estimates of efficacy for microgliosis were much greater than those identified for astrocytosis the two species of cellular infiltrates had a strong correlation with one another. For outcomes in the MWM I found a strong correlation between changes in the acquisition and probe phase which sequentially increased at later acquisition stages.

For relationships between pathological outcomes, changes in plaque pathology were present in all significant relationships, where correlations were found with changes in amyloid beta 40, amyloid beta 42, tau and neurodegeneration. I identified a medium strength correlation between changes in pathology and neurobehaviour and while plaque burden, amyloid beta 40 and amyloid beta 42 could all explain a significant proportion of changes, there may be value in the hypothesis that neurodegeneration provides the best predictor of changes in neurobehaviour.

Overall this chapter provides estimates of efficacy across 12 outcomes and within these I was frequently able to estimate efficacy for individual transgenic groups and specific methodologies. While a number of stratified analyses suggested that methodologies do not impact on observed outcomes (e.g. plaque staining technique, length of amyloid species assessed, size of pool in the MWM) there were also methodologies used which were associated with differences in observed outcomes. For example, data suggested that indirect assessment of neurodegeneration outcomes were associated with greater estimates of effect than direct measures which may be an important consideration to clinical trial design. Perhaps the finding with the greatest continuity was the impact of the transgenic model group used across pathological outcomes (where 4 of a possible 6 stratifications proved significant). Such findings suggest that a deeper understanding of transgenic models themselves may provide insights into intervention efficacy.

Therefore, our next chapter explores the impact of age and sex across the different transgenic mouse models. I also perform analyses specifically on transgenic control mice to aid our understanding of the age, pathology and neurobehaviour collectively.

4.15.2 Implications of findings

Where I inspected relationships within outcomes I identified a number of particularly strong relationships (e.g. plaque burden, amyloid beta 40, cellular infiltrates). I must be cautious in interpretation as observed relationships imply associations, not causations. Nonetheless, it is reassuring with regard to external validity that despite a multitude of methodologies available there, measurements of amyloid and plaques generally correlated extremely well together.

For relationships between pathological outcomes, it is interesting that all statistically significant associations involved plaque burden. Such findings could imply that specific pathological targeting of 'early' amyloid cascade hypothesis targets could have particularly widespread knock on effects. However, one might also expect dominant influences from other outcomes which were not observed: in particular tau pathology. Associations between amyloid and other outcomes may be also be influenced by the prominence of amyloid bearing models.

While there were a number of associations identified between pathological and neurobehavioural outcomes the strongest relationship observed was for neurodegeneration. Few models are capable of capturing such features which is reflected by a low number of publications which report neurodegeneration outcomes. Such data suggest that if I are to assess pathological outcomes as surrogate measures of improvement in behaviour, selecting models capable of capturing neurodegeneration may provide the greatest likelihood of clinical success.

Chapter 5: Age and transgene analyses

Understanding the impact study characteristics exert on observed efficacies is a fundamental aim of this thesis. In this chapter I examine three age related parameters for their observed impact on effect size: (i) the age of mice at intervention administration, (ii) assessment and (iii) the difference between the age at administration and assessment. I additionally assess the impact of sex on observed outcomes.

For age specific analyses I analyse outcome measures datasets overall and I then perform analyses on the specific transgenic model group. For neurobehavioural data I chose to analyse data overall, as I envisaged this would be the most clinical relevant approach, opposed to stratifying data according to the individual paradigm used. I looked to further inform analyses conducted on interventions by assessing the impact of the transgene itself and where age related analyses are conducted within such datasets, quartiles are defined by those used in intervention analyses.

5.1 Age specific analyses for pathological outcomes

For each outcome, I stratify data into inter-quartile ranges to assess the impact of the age at intervention administration, outcome assessment, and the difference between intervention administration and outcome assessment. For age specific analyses, I stratify all data for a given outcome and then explore individual transgenic model groups; to reflect differences in pathologies of the transgenic used. For all analyses, as I must stratify data into four categories, I took a conservative approach and stratify data wherever there were 20 or more experiments. Table 5.1 describes the number of experiments performed across each of the main pathological outcomes according to the transgenic group used. For each outcome, I plot data overall and the most commonly used transgenic, and tabulate others.

	Transgenic model group						
	APP	APPPS	3xTgAD	Tau	PS1	other	Total
Plaque burden	268*	79*	24*	no data	no data	7	378
Amyloid beta 40	292*	61*	33*	1	1	no data	388
Amyloid beta 42	288*	67*	31*	1	1	1	389
Tau	8	4	48*	20*	no data	4	84
Cellular infiltrates	61*	25*	1	2	no data	no data	89
Neurodegeneration	43*	11	1	9	no data	no data	64

Table 5.1: The number of experiments measuring different pathological outcomes according by transgenic model group Where sufficient data were present (> 20 experiments I stratified outcomes according to the transgenic model group used (shown by *).

5.1.1 Age at intervention administration

Plaque burden

For all 378 experiments where plaque burden was stained using immunohistochemically methods it was possible to stratify data according to the age of transgenic at intervention administration. Overall, estimates of effect suggested an inverse relationship between effect size and age at intervention but this did not account for a signification proportion of the observed heterogeneity (χ^2 =2.70, Figure 5.1a, Table 5.2). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Plaque burden individual transgenic model groups

As 268/378 of experiments were performed on APP models I stratified data by interquartile ranges and while the same relationship was observed, this did not account for a significant proportion of the observed heterogeneity (χ^2 =0.36, Figure 5.1b). Sufficient data were also present within the APPPS group where 79 experiments were stratification accounted for a significant proportion of the observed heterogeneity although a linear relationship could not be identified ($p<0.02$, $\chi^2 = 28.7$, Table 5.2). For the 3xTgAD group, stratifying 24 experiments did account for a significant proportion of the observed heterogeneity (χ^2 =25.6, $p<0.02$, Table 5.2) although data were few, particularly in the second quartile and third quartiles (3 experiments respectively).

	Quartiles				Df=3 α=0.02	Critical χ^2 value
	Q1	**Q2**	**Q3**	**Q4**	**All quartiles**	**10.2**
APP	1.31 (0.96 to 1.67) **65**	1.02 (0.75 to 1.28) **70**	0.88 (0.63 to 1.14) **48**	0.86 (0.65 to 1.08) **83**	0.99 (0.86 to 1.12) **268**	Non sig.
Quartiles (days)	0 to 102	112 to 224	238 to 322	336 to 672		
APPPS	0.59 (0.1 to 1.07) **21**	1.12 (0.62 to 1.63) **18**	1.12 (0.51 to 1.73) **22**	0.85 (0.39 to 1.31) **18**	0.91 (0.65 to 1.17) **79**	Sig.
Quartiles (days)	21 to 56	63 to 140	168 to 217	224 to 448		
3xTgAD	1.16 (0.44 to 1.88) **9**	-0.28 (-1.99 to 1.43) **3**	1.72 (-1.19 to 4.64) **3**	1.98 (0.58 to 3.38) **9**	1.11 (0.46 to 1.75) **24**	Sig
Quartiles (days)	28 to 84	98 to 112	168 only	336 to 504		
Data overall	**1.08 (0.83 to 1.32) 104**	**1 (0.71 to 1.29) 75**	**0.96 (0.75 to 1.18) 98**	**0.91 (0.70 to 1.11) 100**	**0.98 (0.87 to 1.1) 378**	Non sig **(11.3 crit)**.
Quartiles (days)	**0 to 84**	**98 to 182**	**196 to 322**	**336 to 672**		

Table 5.2: Plaque burden outcomes were stratified by the age at administration overall, and by specific transgenic model groups (APP, APPPS and 3xTgAD). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

Amyloid beta 40

For 96% (374/388) of amyloid beta 40 experiments it was possible to stratify data according to the age of transgenic at intervention administration. Overall, stratifying amyloid beta 40 by the interquartile range did accounted for a significant proportion of the observed heterogeneity ($\chi^2 = 13.2$, Figure 5.1c), but I did not identify a specific relationship between point estimates and age. I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Amyloid beta 40 individual transgenic model group analyses

As 278/374 experiments were performed on APP models I stratified data according to the age at intervention administration but this did not account for a significant proportion of the observed heterogeneity (χ^2 =8.55, Figure 5.1d). For the 61 experiments which were performed on APPPS mice I stratified data by age at administration but this did not explain a significant proportion of observed heterogeneity. (χ^2 =7.32, Table 5.3). There were also sufficient data to stratify 3xTgAD outcomes (33 experiments) although there was no clear relationship between age at intervention administration and effect size ($p<0.02$, χ^2=13.6, Table 5.3).

	Quartiles				df=3 α=0.02	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	10.2
APP	0.92 (0.52 to 1.31) **64**	0.74 (0.49 to 0.99) **71**	0.77 (0.53 to 1.01) **76**	0.49 (0.3 to 0.68) **67**	0.71 (0.58 to 0.84) **278**	**Non. Sig.**
Quartiles (days)	0 to 77	84 to 140	168 to 280	294 to 672		
APPPS	0.56 (-0.03 to 1.15) **17**	0.74 (0.32 to 1.16) **14**	0.55 (0.12 to 0.98) **17**	0.37 (-0.15 to 0.9) **13**	0.55 (0.31 to 0.8) **61**	**Non. sig.**
Quartiles (days)	21 to 56	60 to 69	70 to 140	169 to 616		
3xTgAD	0.59 (-0.53 to 1.71) **3**	0.46 (0.19 to 0.72) **14**	-0.09 (-0.77 to 0.58) **8**	0.36 (-0.23 to 0.96) **8**	0.32 (0.05 to 0.6) **33**	**Sig.**
Quartiles (days)	28 to 56	84 to 98	112 to 168	280 to 644		
Data overall	0.79 (0.51 to 1.07) **96**	0.56 (0.36 to 0.75) **86**	0.73 (0.51 to 0.96) **84**	0.53 (0.36 to 0.7) **108**	0.64 (0.54 to 0.75) **374**	**Sig. (11.3 crit)**
Quartiles (days)	**0 to 70**	**77 to 126**	**140 to 263**	**280 to 672**		

Table 5.3 Amyloid beta 40 outcomes were stratified by the age at administration overall, and by specific transgenic model groups (APP, APPPS and 3xTgAD). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

Amyloid beta 42

For 99.7% (388/389) of amyloid beta 42 experiments it was possible to stratify data according to the age of transgenic at intervention administration. Overall, stratifying amyloid beta 42 data according to the age at intervention administration did not account for a significant proportion of the observed heterogeneity, although there did appear to be a modest inverse relationships between effect size and age (χ^2 =7.21, Figure 5.1e). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

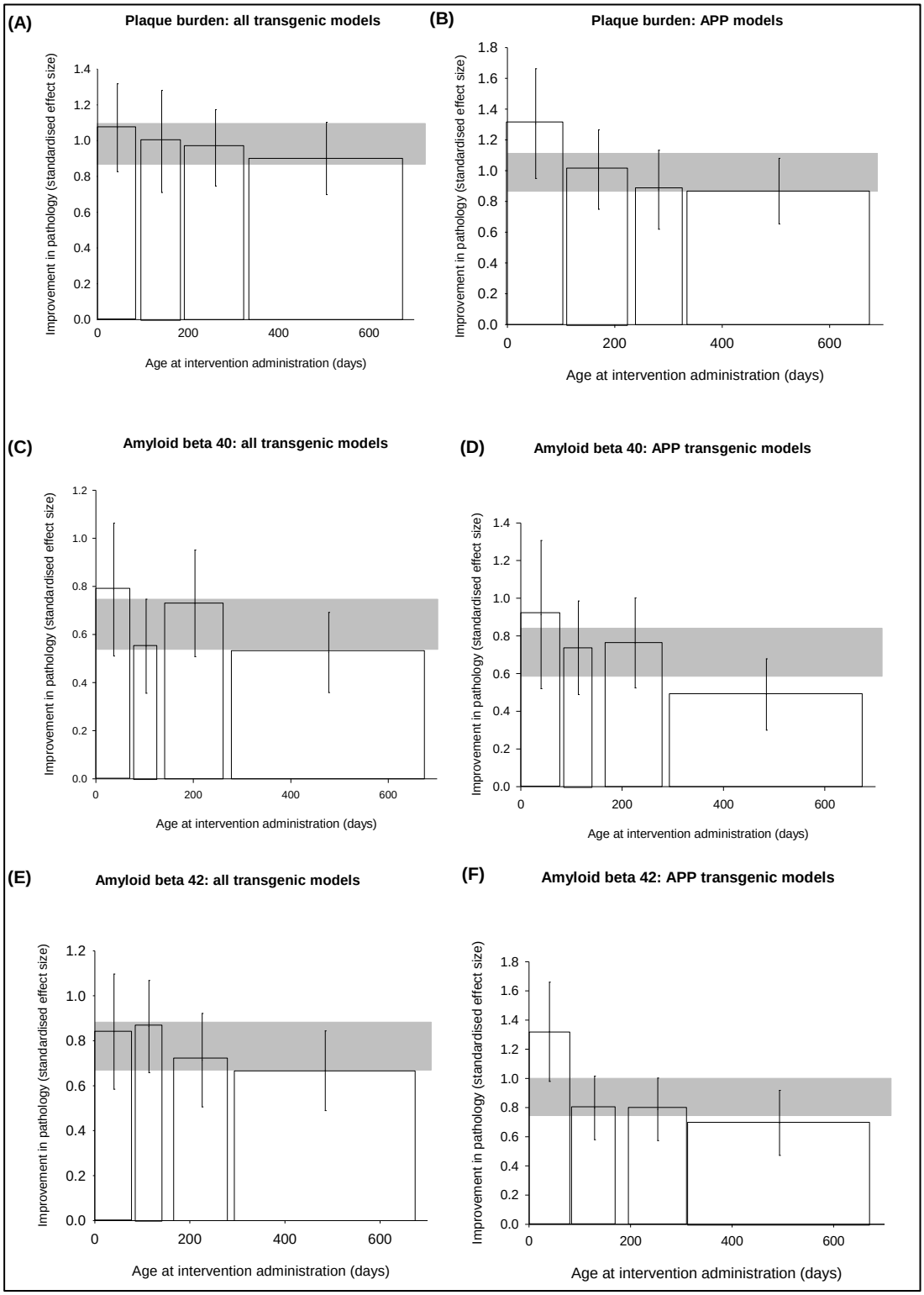
Amyloid beta 42 individual transgenic model groups

When I inspected data from the APP transgenic group I observed higher estimates of efficacy at earlier ages of intervention administration and this accounted for a significant proportion of the observed heterogeneity (χ^2 = 12.7, p<0.02, Figure 5.1f). Where I stratified APPPS and 3xTgAD according to the age at intervention assessment this did not account for a significant proportion of the observed heterogeneity (χ^2 = 9.91, and χ^2 =4.5 respectively).

	Quartiles				df=3 α=0.02	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	10.2
APP	1.33 (0.99 to 1.67) **79**	0.8 (0.59 to 1.02) **64**	0.79 (0.58 to 1.01) **76**	0.7 (0.48 to 0.92) **68**	0.88 (0.75 to 1) **287**	**Sig.**
Quartiles (days)	**0 to 77**	**84 to 171**	**168 to 308**	**311 to 672**		
APPPS	0.65 (0.15 to 1.14) **18**	0.69 (0.31 to 1.06) **14**	0.84 (0.27 to 1.4) **16**	0.36 (-0.06 to 0.77) **19**	0.61 (0.37 to 0.84) **67**	**Non. sig.**
Quartiles (days)	**21 to 49**	**56 to 70**	**84 to 140**	**168 to 616**		
3xTgAD	0.42 (-0.23 to 1.07) **3**	0.19 (-0.07 to 0.46) **13**	0.19 (-0.85 to 1.24) **7**	0.44 (0.07 to 0.81) **8**	0.31 (0.03 to 0.59) **31**	**Non. sig.**
Quartiles (days)	**28 to 56**	**84 only**	**98 to 169**	**260 to 644**		
Data overall	**0.84 (0.59 to 1.1) 81**	**0.87 (0.66 to 1.07) 120**	**0.72 (0.51 to 0.93) 94**	**0.67 (0.49 to 0.85) 93**	**0.78 (0.67 to 0.88) 388**	**Non. sig. (11.3 crit)**
Quartiles (days)	**0 to 77**	**84 to 140**	**168 to 280**	**294 to 672**		

Table 5.4 Amyloid beta 42 outcomes were stratified by the age at administration overall, and by specific transgenic model groups (APP, APPPS and 3xTgAD). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

Figure 5.1 (next page): I stratified pathological outcomes according to the age at which interventions were administered. Stratified summary estimates are given for each quartile for plaque burden, amyloid beta 40 and amyloid beta 42 for all transgenic models (A, C, E) and for the most frequently used transgenic models (B, D,F). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.


(A)
Plaque burden: all transgenic models
Improvement in pathology (standardised effect size)
Age at intervention administration (days)
(B)
Plaque burden: APP models
Improvement in pathology (standardised effect size)
Age at intervention administration (days)
(C)
Amyloid beta 40: all transgenic models
Improvement in pathology (standardised effect size)
Age at intervention administration (days)
(D)
Amyloid beta 40: APP transgenic models
Improvement in pathology (standardised effect size)
Age at intervention administration (days)
(E)
Amyloid beta 42: all transgenic models
Improvement in pathology (standardised effect size)
Age at intervention administration (days)
(F)
Amyloid beta 42: APP transgenic models
Improvement in pathology (standardised effect size)
Age at intervention administration (days)

Tau

Overall, stratifying tau outcomes did not account for a significant proportion of the observed heterogeneity (χ^2 =10.17, Figure 5.2a), although there did appear to be an inverse relationship between effect size and age at intervention.

Tau individual transgenic model groups

As 48 experiments were performed on the 3xTgAD transgenic model I stratified data by interquartile ranges and this did not account for a significant proportion of the observed heterogeneity (χ^2 = 7.05, Figure 5.2b). For the 20 experiments performed using tau transgenics, stratifying data did account for a significant proportion of the observed heterogeneity however the overall relationship was unclear (χ^2 = 13.0).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Tau	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
3xTgAD	0.18 (-0.39 to 0.75) **6**	0.89 (0.41 to 1.36) **19**	0.87 (0.29 to 1.44) **15**	0.21 (-0.22 to 0.65) **8**	0.56 (0.32 to 0.81) **48**	**Non. Sig.**
Quartiles (days)	28 to 56	84 to 140	168 to 336	364 to 644		
Tau	2.79 (-0.1 to 5.69) **4**	0.35 (0.11 to 0.58) **6**	0.53 (0.19 to 0.86) **5**	1.21 (0.18 to 2.23) **5**	0.63 (0.36 to 0.9) **20**	**Sig.**
Quartiles (days)	0 only	56 only	140 to 229	252 to 504		
Data overall	0.35 (0.08 to 0.62) **18**	0.62 (0.25 to 0.99) **26**	0.54 (0.25 to 0.83) **15**	0.7 (0.33 to 1.08) **25**	0.55 (0.38 to 0.72) **84**	**Non. sig. (11.3 crit)**
Quartiles (days)	0 to 56	84 to 168	224 to 308	336 to 644		

Table 5.5 Tau outcomes were stratified by the age at administration overall, and by specific transgenic model groups (3xTgAD and tau). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

Cellular infiltrates

Overall, stratifying cellular infiltrate outcomes by the interquartile accounted for a significant proportion of the observed heterogeneity with later ages of intervention administration associated with an increase in cell infiltrates ($\chi^2 = 176$, $p<0.01$, Figure 5.2c).

Cellular infiltrates transgenic model groups

As 61/88 experiments were performed on APP models I stratified data according to the age of the mice at intervention administration although relationships were difficult to define ($\chi^2 = 121$, $p<0.02$, Figure 5.2d). For the APPPS group, 25 experiments the overall relationship was without a specific direction (data formed a V shaped plot, $\chi^2 = 82.7$, $p<0.02$, Table 5.6).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Cellular infiltrates	**Q1**	**Q2**	**Q3**	**Q4**	**All quartiles**	**10.2**
APP	0.42 (-0.15 to 0.99) **17**	1.35 (0.76 to 1.94) **13**	0.33 (-0.59 to 1.25) **14**	-0.58 (-1.14 to -0.03) **17**	0.34 (-0.02 to 0.7) **61**	**Sig.**
Quartiles (days)	30 to 140	168 to 280	308 to 462	476 to 672		
APPPS	0.64 (0.07 to 1.21) **7**	0.67 (0.16 to 1.18) **3**	0.13 (-1.47 to 1.74) **9**	0.47 (-0.17 to 1.11) **6**	0.51 (0.02 to 0.99) **25**	**Sig.**
Quartiles (days)	**42 to 84**	**140 to 168**	**196 to 224**	**231 to 336**		
Data overall	0.69 (0.29 to 1.08) 22	0.32 (-0.32 to 0.97) 22	1.18 (0.62 to 1.74) 22	-0.59 (-1.03 to -0.15) 22	0.41 (0.12 to 0.69) 88	**Sig. (11.3 crit).**
Quartiles (days)	14 to 119	140 to 238	252 to 392	406 to 672		

Table 5.6: Cellular infiltrate outcomes were stratified by the age at administration overall, and by specific transgenic model groups (APP and APPPS). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

Neurodegeneration

Overall, stratifying neurodegeneration outcomes did not account for a significant proportion of the observed heterogeneity, although there did appear to be a modest reduction in effect size when interventions were administered within the first quartile (χ^2 = 7.34, Figure 5.2e).

Neurodegeneration outcomes by transgenic model groups

There were only sufficient data (42 experiments) to inspect data from the APP transgenic group for the impact of the age at intervention administration. When I inspected data from the APP transgenic group, estimates of efficacy were smaller in the first quartile but stratification did not prove significant (χ^2 =4.17, Figure 5.2f).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Neurodegeneration	**Q1**	**Q2**	**Q3**	**Q4**	**All quartiles**	**10.2**
APP	0.48 (-0.01 to 0.96) **12**	1.53 (0.86 to 2.21) **11**	0.77 (0.43 to 1.11) **13**	0.84 (0.02 to 1.65) **6**	0.84 (0.58 to 1.1) **42**	**Non.Sig.**
Quartiles (days)	**21 to 84**	**112 to 280**	**336 only**	**364 to 504**		
Data overall	0.56 (0.12 to 0.99) **14**	1.56 (1 to 2.13) **17**	0.84 (0.48 to 1.2) **9**	0.86 (0.57 to 1.15) **22**	0.94 (0.72 to 1.15) **62**	**Non sig. (11.3 crit).**
Quartiles (days)	**14 to 84**	**112 to 224**	**238 to 308**	**336 to 616**		

Table 5.7: Neurodegeneration outcomes were stratified by the age at administration overall, and by specific transgenic model groups (APP only). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

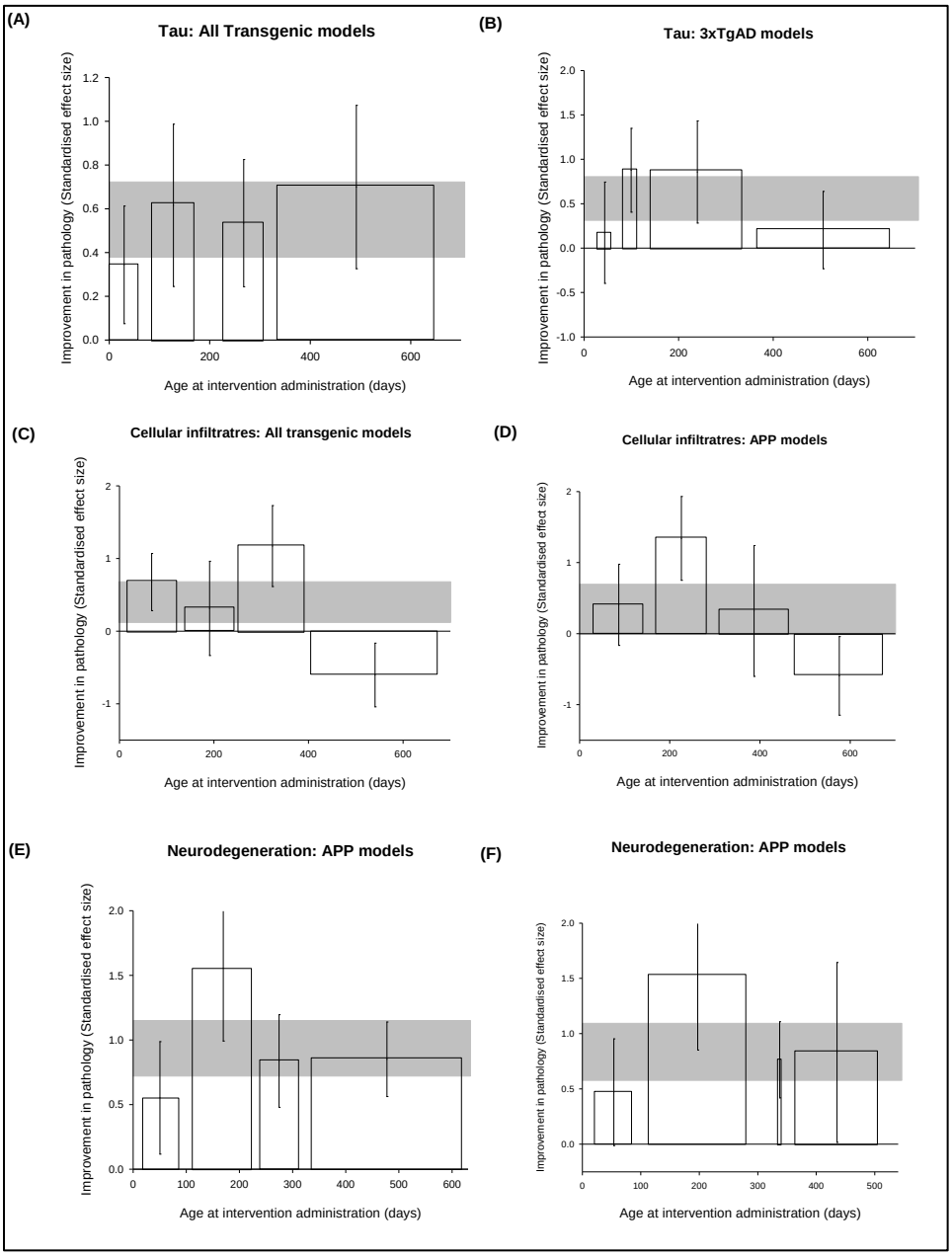


Figure 5.2: I stratified pathological outcomes according to the age at which interventions were administered. Stratified summary estimates are given for each quartile for tau, cellular infiltrates and neurodegeneration for all transgenic models (A, C, E) and for the most frequently used transgenic models (B, D,F). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

5.1.2 Age at outcome assessment

Plaque burden

Overall I assessed 99% (376/378) of the plaque burden dataset for the impact of age of outcome assessment. Overall, stratifying data according to the age at which outcomes were assessed did not account for a significant proportion of the observed heterogeneity. I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Plaque burden individual transgenic model groups

I assessed the impact of the age at outcome assessment for the 266 experiments which used APP mice, but this did not account for a significant proportion of the observed heterogeneity (χ^2 =6.51). In contrast, for the 79 experiments reported from APPPS mice, stratifying data according to the age at outcome assessment did account for a significant proportion of the heterogeneity (χ^2 =43.3, p<0.02, Table 5.8) but relationships were difficult to define .Twenty-four plaque burden experiments were performed within the 3xTgAD group and our stratified analysis suggested that very early estimates were lower than others, crossing the line of no effect (χ^2 =35.2, p<0.02, Table 5.8).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Plaque burden	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	1.29 (0.97 to 1.61) **68**	0.68 (0.44 to 0.93) **68**	1.07 (0.83 to 1.31) **65**	0.98 (0.72 to 1.25) **65**	0.99 (0.85 to 1.12) **266**	**Non. Sig.**
Quartiles (days)	66 to 231	252 to 364	368 to 469	476 to 721		
APPPS	1.14 (0.68 to 1.6) **20**	0.27 (-0.13 to 0.68) **20**	1.1 (0.57 to 1.64) **19**	0.89 (0.31 to 1.47) **20**	0.91 (0.65 to 1.17) **79**	**Sig.**
Quartiles (days)	65 to 210	211 to 252	266 to 336	364 to 560		
3xTgAD	0.29 (-0.6 to 1.19) **8**	1.25 (-0.65 to 3.15) **4**	2.54 (1.08 to 3.99) **8**	1.23 (0.56 to 1.89) **4**	1.11 (0.46 to 1.75) **24**	**Sig.**
Quartiles (days)	120 to 168	175 to 210	252 to 343	366 to 517		
Data overall	1.2 (0.94 to 1.46) **96**	0.82 (0.59 to 1.05) **85**	1.01 (0.76 to 1.25) **101**	0.91 (0.71 to 1.11) **94**	0.98 (0.86 to 1.1) **376**	**Non. Sig. (11.3 crit).**
Quartiles (days)	65 to 210	211 to 322	336 to 434	435 to 721		

Table 5.8: Plaque burden outcomes were stratified by the age at outcome assessment overall, and by specific transgenic model groups (APP, APPPS and 3xTgAD). Estimates of efficacy are given in standardised effect size, brackets give 95% CI and number in bold represents the total number of experiments.

Amyloid beta 40

373/388 amyloid beta 40 experiments stated the age at outcome assessment and were taken forward to stratified analysis. Stratifying data according to the age at outcome assessment did not account for a significant proportion of the observed heterogeneity but I observed smaller estimates of efficacy at later ages of assessment (χ^2 =35.2, p<0.01, Figure 5.3). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Amyloid beta 40 and individual transgenic model groups

I identified that amyloid beta 40 was most commonly assessed in APP transgenic models (277 experiments) and stratifying data according to the age at outcome assessment accounted for a significant proportion of the observed heterogeneity although there was no clear relationship(χ^2 =22.8, p<0.02, Figure 5.3).

There were also sufficient data present in both APPPS and 3xTgAD transgenic groups, but stratifying data according to the age at outcome assessment did not prove statistically significant (χ^2 =8.53 and χ^2 =2.96 respectively).

	Quartiles				df=3 α=0.02	Critical χ^2 Value
	Q1	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	0.61 (0.28 to 0.94) **68**	1.01 (0.74 to 1.28) **69**	0.73 (0.47 to 0.99) **71**	0.53 (0.34 to 0.72) **69**	0.72 (0.59 to 0.84) **277**	**Sig.**
Quartiles (days)	51 to 113	115 to 290	308 to 406	413 to 714		
APPPS	0.94 (0.34 to 1.53) **16**	0.64 (0.26 to 1.01) **15**	0.47 (-0.19 to 1.13) **15**	0.24 (-0.13 to 0.62) **15**	0.55 (0.31 to 0.8) **61**	**Non. Sig.**
Quartiles (days)	56 to 112	120 to 210	224 to 300	301 to 672		
3xTgAD	0.17 (-0.22 to 0.56) **9**	0.29 (-0.52 to 1.09) **8**	0.35 (-0.14 to 0.83) **8**	0.54 (-0.11 to 1.2) **8**	0.32 (0.05 to 0.6) **33**	**Non. Sig.**
Quartiles (days)	112 to 168	210 to 289	336 to 448	450 to 672		
Data overall	0.7 (0.44 to 0.97) **92**	0.75 (0.53 to 0.97) **98**	0.66 (0.44 to 0.88) **93**	0.51 (0.35 to 0.68) **90**	0.65 (0.54 to 0.75) **373**	**Non. Sig. (11.3 crit).**
Quartiles (days)	**51 to 119**	**120 to 280**	**281 to 392**	**393 to 714**		

Table 5.9: Amyloid beta 40 outcomes were stratified by the age at outcome assessment overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

Amyloid beta 42

For 387/389 amyloid beta 42 experiments it was possible to stratify data according to the age at outcome assessment. Overall, I identified that stratifying data by the age at outcome assessment did not account for significant proportion of the observed heterogeneity (χ^2 =7.5, Figure 5.3). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

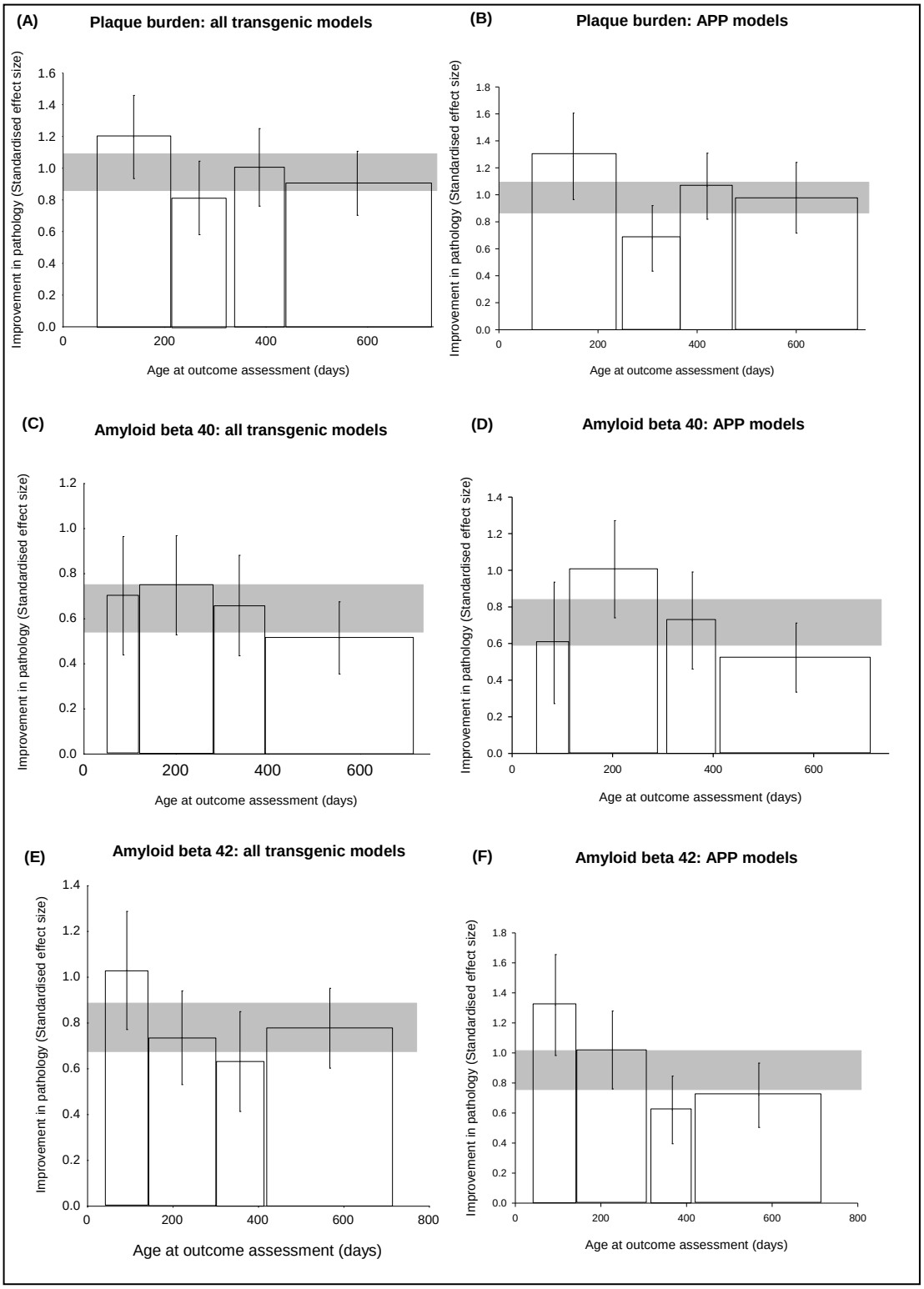
Amyloid beta 42 and individual transgenic model groups

I stratified data according to the age of outcome assessment in APP mice and identified that smaller estimates of efficacy were associated with later ages at outcome assessment (χ^2 =21.3, p<0.02, Figure 5.3). Conversely, for the 3xTgAD group 31 experiments suggested that higher estimates of efficacy were associated with later ages of assessment (χ^2 =12.9, p<0.02, Table 5.10). I also stratified APPPS (67 experiments) but this did not account for a significant proportion of the observed heterogeneity (χ^2 =1.12, Table 5.10).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Amyloid beta 42	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	1.32 (0.99 to 1.66) **72**	1.02 (0.77 to 1.28) **71**	0.63 (0.4 to 0.85) **79**	0.72 (0.51 to 0.94) **64**	0.88 (0.76 to 1.01) **286**	**Sig.**
Quartiles (days)	42 to 141	142 to 308	317 to 413	420 to 714		
APPPS	0.69 (0.24 to 1.13) **17**	0.56 (0.3 to 0.82) **17**	0.37 (-0.24 to 0.99) **16**	0.79 (0.22 to 1.36) **17**	0.61 (0.37 to 0.84) **67**	**Non. Sig.**
Quartiles (days)	56 to 112	120 to 224	231 to 300	301 to 627		
3xTgAD	0 (-0.48 to 0.48) **9**	0.3 (-0.52 to 1.12) **6**	0.14 (-0.23 to 0.52) **8**	0.85 (0.24 to 1.45) **8**	0.31 (0.03 to 0.59) **31**	**Sig.**
Quartiles (days)	112 to 168	210 to 252	336 to 448	450 to 672		
Data overall	1.03 (0.77 to 1.29) **97**	0.74 (0.53 to 0.94) **97**	0.63 (0.41 to 0.85) **94**	0.78 (0.6 to 0.95) **99**	0.78 (0.67 to 0.88) **387**	**Non. sig. (11.3 crit)**
Quartiles (days)	43 to 141	142 to 300	301 to 413	420 to 714		

Table 5.10 Amyloid beta 42 outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments

Figure 5.3 (next page): I stratified pathological outcomes according to the age at which outcomes were assessed. Stratified summary estimates are given for each quartile for plaque burden, amyloid beta 40 and amyloid beta 42 for all transgenic models (A, C, E) and for the most frequently used transgenic models (B, D,F). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.


(A)
Plaque burden: all transgenic models
Improvement in pathology (Standardised effect size)
Age at outcome assessment (days)
(B)
Plaque burden: APP models
Improvement in pathology (Standardised effect size)
Age at outcome assessment (days)
(C)
Amyloid beta 40: all transgenic models
Improvement in pathology (Standardised effect size)
Age at outcome assessment (days)
(D)
Amyloid beta 40: APP models
Improvement in pathology (Standardised effect size)
Age at outcome assessment (days)
(E)
Amyloid beta 42: all transgenic models
Improvement in pathology (Standardised effect size)
Age at outcome assessment (days)
(F)
Amyloid beta 42: APP models
Improvement in pathology (Standardised effect size)
Age at outcome assessment (days)

Tau

I stratified the 84 tau experiments to assess the impact of the age at outcome assessment but this did not account for a significant proportion of the observed heterogeneity (χ^2 =9.14, Figure 5.4)

Tau and individual transgenic model groups

For the 3xTgAD group there were sufficient data to allow stratification of data by the age at outcome assessment (48 experiments) but this did not account for a significant proportion of the observed heterogeneity (χ^2 =7.65, Figure 5.4). Conversely, stratifying data from the tau transgenic group did account for a significant proportion of the observed heterogeneity (χ^2 =12.37, p<0.02, Table 5.11), although there was no clear relationship.

	Quartiles				df=3 α=0.02	Critical χ^2 value
Tau	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
3xTgAD	0.75 (0.02 to 1.48) **12**	0.75 (0.27 to 1.23) **12**	0.94 (0.22 to 1.66) **12**	0.31 (-0.05 to 0.66) **12**	0.56 (0.32 to 0.81) **48**	**Non. sig.**
Quartiles (days)	120 to 231	252 to 336	339 to 381	420 to 672		
Tau	0.33 (-0.16 to 0.82) **5**	0.37 (0.1 to 0.63) **7**	0.65 (0.33 to 0.98) **3**	1.21 (0.18 to 2.23) **5**	0.63 (0.36 to 0.9) **20**	**Sig.**
Quartiles (days)	140 to 168	224 to 252	294 to 308	336 to 546		
Data overall	0.52 (0.14 to 0.9) 22	0.67 (0.36 to 0.97) 20	0.45 (0.06 to 0.84) 21	0.57 (0.24 to 0.91) 21	0.55 (0.38 to 0.72) 84	**Non. sig. (11.3 crit).**
Quartiles (days)	71 to 224	231 to 320	336 to 381	389 to 672		

Table 5.11 Tau outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine the 3xTgAD and tau transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments

Cellular infiltrates

For outcome regarding cellular infiltrates it was possible to determine the age at outcome assessment for 87/89 experiments. Where I stratified such data according to the age at outcome assessment, later ages of assessment were associated with smaller estimates of effect size (χ^2 =30.7, p<0.01, Figure 5.4).I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Cellular infiltrates and individual transgenic model groups

I inspected the APP group for the impact the age of assessment has on outcomes and identified that earlier ages of outcome assessment were associated with greater reductions of cellular infiltrate species (χ^2 =82.7, p<0.02, Figure 5.4). I did not identify a significant impact of the age of assessment within APPPS models (χ^2 =8.65).

	Quartiles				df=3 α=0.02	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	10.2
APP	0.88 (0.31 to 1.44) **16**	0.49 (-0.09 to 1.07) **14**	-0.12 (-0.61 to 0.37) **17**	0.04 (-1.19 to 1.26) **13**	0.35 (-0.01 to 0.72) **60**	**Sig.**
Quartiles (days)	112 to 287	308 to 433	445 to 504	507 to 714		
APPPS	0.75 (0.38 to 1.13) **7**	0.55 (-0.25 to 1.35) **5**	-0.34 (-1.31 to 0.63) **8**	1.67 (0.13 to 3.22) **5**	0.51 (0.02 to 0.99) **25**	**Non. sig.**
Quartiles (days)	70 to 220	252 to 280	301 to 336	363 to 504		
Data overall	0.77 (0.37 to 1.17) **24**	0.73 (0.13 to 1.32) **20**	0.02 (-0.42 to 0.46) **21**	0.09 (-0.72 to 0.89) **22**	0.42 (0.13 to 0.7) **87**	**Sig. (11.3 crit).**
Quartiles (days)	35 to 252	258 to 364	371 to 483	493 to 714		

Table 5.12 Cellular infiltrates outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP and APPPS transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

Neurodegeneration

For 62 out of 64 neurodegeneration experiments it was possible to assess the impact of the age at outcome assessment but this did not account for a significant proportion of the observed heterogeneity (χ^2 =3.08, Figure 5.4). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Neurodegeneration and individual transgenic model groups

For neurodegeneration outcomes, APP was the only transgenic group where sufficient data were present to allow stratification by the age at outcome assessment. Stratifying such data did not account for a significant proportion of the observed heterogeneity (χ^2 =6.09, Figure 5.4) and estimates of efficacy within each quartile did not suggest any particular relationships.

	Quartiles				df=3 α=0.02	Critical χ^2 value
Neurodegeneration	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	1.2 (0.39 to 2) 12	0.58 (0.31 to 0.84) 9	1 (0.46 to 1.54) 6	0.76 (0.43 to 1.08) 15	0.84 (0.58 to 1.1) 42	**Non. Sig.**
Quartiles (days)	112 to 252	260 to 364	371 to 493	504 to 630		
Data overall	1.3 (0.63 to 1.97) 16	0.88 (0.49 to 1.28) 15	0.88 (0.56 to 1.2) 15	0.79 (0.46 to 1.12) 16	0.94 (0.72 to 1.15) 62	**Non. Sig. (11.3 crit).**
Quartiles (days)	35 to 231	238 to 308	318 to 493	504 to 651		

Table 5.13 Neurodegeneration outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine the APP transgenic group in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

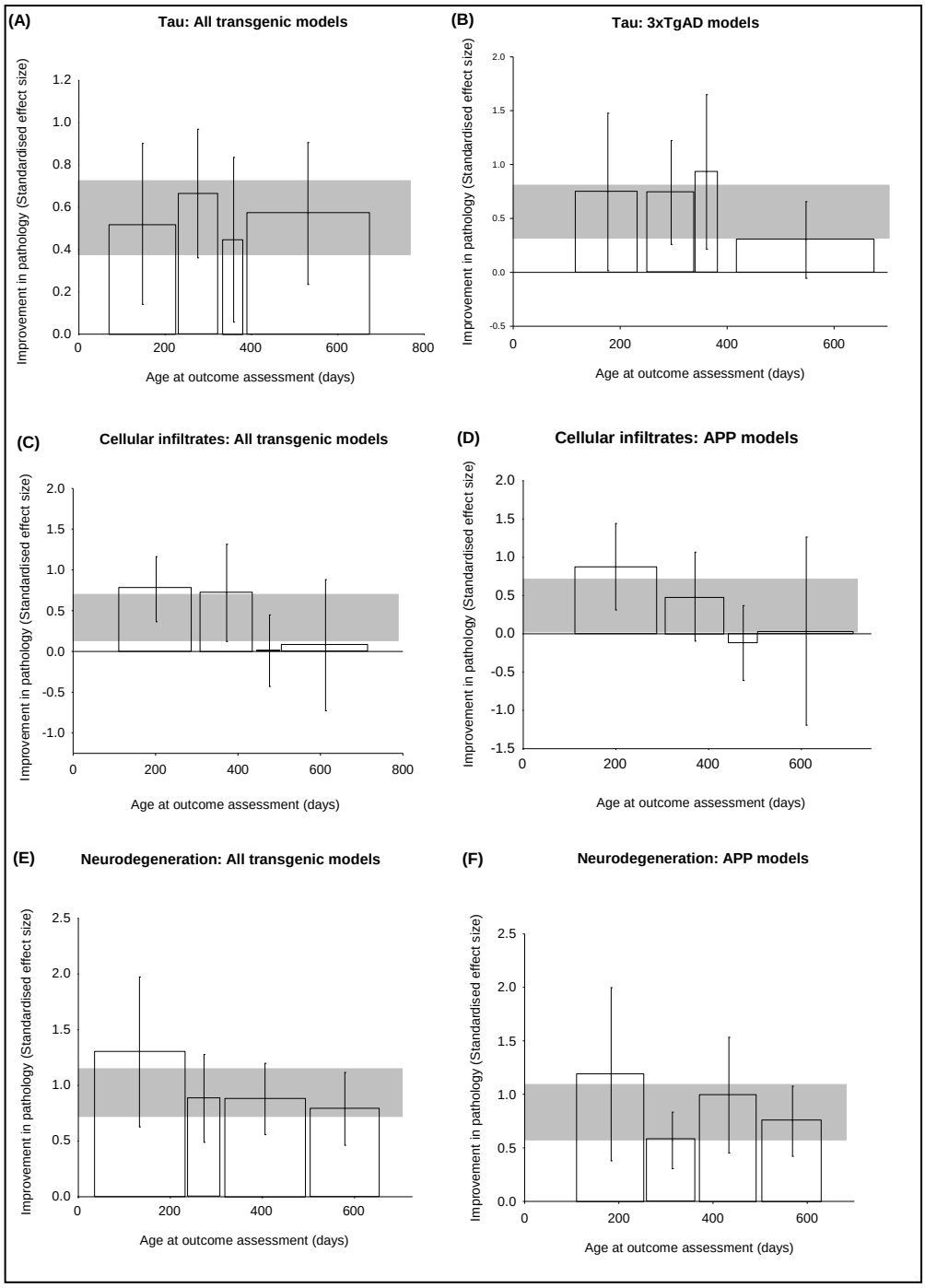


Figure 5.4: I stratified pathological outcomes according to the age of outcome assessment. Stratified summary estimates are given for each quartile for tau, cellular infiltrates and neurodegeneration for all transgenic models (A, C, E) and for the most frequently used transgenic models (B, D,F). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

5.1.3 Difference between age at administration and age at assessment

Plaque burden

For plaque burden outcomes, it was possible to stratify 376/378 of experiments according to the difference between age at administration and assessment. Stratifying data accounted for a significant proportion of the observed heterogeneity and estimates of efficacy showed a modest inverse relationship with the difference between age at administration and assessment (χ^2 =18.7, p<0.01, Figure 5.5).

Plaque burden and individual transgenic model groups

I stratified the 266 APP experiments according to the difference between age at administration and assessment but this did not account for a significant proportion of heterogeneity (χ^2 =0.24, Figure 5.5). Similarly, stratifying the 79 APPPS transgenic experiments did not account for a significant proportion of the observed heterogeneity (χ^2 =5.49, Table 5.14). I stratified 24 3xTgAD experiments where there was no clear relationship between estimates of efficacy and the difference between age at administration and assessment (χ^2 =47.5, p<0.02, Table 5.14).

Amyloid beta 40

For amyloid beta 40 outcomes it was possible to stratify 373 experiments according to the difference between age at administration and assessment. Stratifying data overall did not account for a significant proportion of the observed heterogeneity (χ^2 =8.12). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

	Quartiles				df=3 α=0.02	Critical χ^2 value
Plaque burden	**Q1**	**Q2**	**Q3**	**Q4**	**All quartiles**	**10.2**
APP	0.96 (0.67 to 1.25) **72**	1.05 (0.78 to 1.32) **62**	1 (0.71 to 1.28) **50**	0.97 (0.73 to 1.2) **82**	0.99 (0.85 to 1.12) **266**	**Non. Sig.**
Quartiles (days)	2 to 35	36 to 88	89 to 167	168 to 472		
APPPS	0.82 (0.41 to 1.23) **22**	1.1 (0.52 to 1.68) **18**	0.88 (0.22 to 1.53) **20**	0.68 (0.31 to 1.06) **19**	0.91 (0.65 to 1.17) **79**	**Non. Sig.**
Quartiles (days)	2 to 28	30 to 105	112 to 196	203 to 420		
3xTgAD	4.52 (1.64 to 7.4) **8**	-0.4 (-1.54 to 0.74) **4**	1.21 (0.34 to 2.08) **7**	1.31 (0.55 to 2.06) **5**	1.11 (0.46 to 1.75) **24**	**Sig.**
Quartiles (days)	3 to 7	8 to 42	45 to 84	112 to 419		
Data overall	1.15 (0.89 to 1.42) **95**	0.92 (0.69 to 1.16) **97**	1.02 (0.83 to 1.22) **109**	0.86 (0.61 to 1.11) **75**	0.98 (0.86 to 1.1) **376**	**Sig.** (11.3 crit).
Quartiles (days)	2 to 32	35 to 84	87 to 168	172 to 472		

Table 5.14 Plaque burden outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

Amyloid beta 40 and individual transgenic model groups

For the 277 experiments which reported amyloid beta 40 outcomes from APP transgenic models I identified a modest increase in effect size with greater differences between the age at administration and outcome assessment (χ^2 =12.38, p<0.02, Figure 5.5). Stratifying 61 APPPS experiments accounted for a significant proportion of heterogeneity but this was not reflected by a relationship between effect size and difference between age at administration and assessment (χ^2 =11.39, p<0.02, Table 5.15). Stratifying 33 3xTgAD experiments did not account for significant proportion of heterogeneity (χ^2 =3.63, Table 5.15).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Amyloid beta 40	**Q1**	**Q2**	**Q3**	**Q4**	**All quartiles**	**10.2**
APP	0.67 (0.39 to 0.95) **65**	0.5 (0.26 to 0.73) **74**	0.89 (0.63 to 1.15) **67**	0.78 (0.53 to 1.03) **71**	0.72 (0.59 to 0.84) **277**	**Sig.**
Quartiles (days)	0 to 6	7 to 56	60 to 133	140 to 396		
APPPS	0.63 (0.04 to 1.22) **15**	0.9 (0.47 to 1.33) **17**	0.36 (-0.04 to 0.76) **14**	0.29 (-0.26 to 0.85) **15**	0.55 (0.31 to 0.8) **61**	**Sig.**
Quartiles (days)	0 to 15	21 to 84	91 to 154	168 to 392		
3xTgAD	0.05 (-0.29 to 0.39) **8**	0.47 (-0.27 to 1.21) **9**	0.44 (-0.27 to 1.15) **8**	0.54 (0 to 1.08) **8**	0.32 (0.05 to 0.6) **33**	**Non. Sig.**
Quartiles (days)	7 to 30	42 to 112	119 to 168	252 to 419		
Data overall	0.59 (0.36 to 0.83) **95**	0.52 (0.32 to 0.71) **90**	0.77 (0.57 to 0.97) **97**	0.67 (0.45 to 0.9) **91**	0.65 (0.54 to 0.75) **373**	**Non. Sig.** (11.3 crit).
Quartiles (days)	0 to 10	11 to 78	84 to 140	149 to 419		

Table 5.15 Amyloid beta 40 outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments

Amyloid beta 42

Stratifying 387 amyloid beta 42 experiments according to the difference between age at administration and outcome assessment did not account for a significant proportion of the observed heterogeneity(χ^2 =4.50, Figure 5.5). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Amyloid beta 42 and individual transgenic model groups

Stratifying APP transgenic models (286 experiments) was weakly associated with smaller estimates of efficacy (χ^2 =21.2, p<0.02, Figure 5.5). For APPPS models, I stratified 67 studies according to the difference between age at intervention administration and outcome assessment but this did not account for a significant proportion of the observed heterogeneity (χ^2 =4.78, Table 5.16). For the 31 experiments examining amyloid beta 42 in 3xTgAD models, larger differences between intervention administration and outcome assessment were weakly associated with higher estimates of efficacy but this was not statistically significant (χ^2 =9.24, p<0.02, Table 5.16)

	Quartiles				df=3 α=0.02	Critical χ^2 value
Amyloid beta 42	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	1.24 (0.93 to 1.56) **71**	0.52 (0.28 to 0.76) **65**	1.01 (0.77 to 1.25) **78**	0.78 (0.55 to 1.02) **72**	0.88 (0.76 to 1.01) **286**	**Sig.**
Quartiles (days)	0 to 20	21 to 76	84 to 153	154 to 396		
APPPS	0.39 (-0.02 to 0.8) **19**	0.82 (0.47 to 1.18) **16**	0.52 (0.21 to 0.84) **15**	0.7 (0.02 to 1.39) **17**	0.61 (0.37 to 0.84) **67**	**Non. Sig.**
Quartiles (days)	0 to 15	21 to 84	91 to 154	168 to 420		
3xTgAD	-0.1 (-0.49 to 0.29) **8**	0.76 (0.02 to 1.49) **8**	0.18 (-0.2 to 0.55) **7**	0.52 (-0.22 to 1.27) **8**	0.31 (0.03 to 0.59) **31**	**Non. Sig.**
Quartiles (days)	7 to 30	42 to 84	112 to 168	252 to 419		
Data overall	0.89 (0.64 to 1.13) 98	0.7 (0.52 to 0.89) 106	0.84 (0.64 to 1.04) 86	0.72 (0.5 to 0.93) 97	0.78 (0.67 to 0.88) **387**	**Non. Sig.** (11.3 crit).
Quartiles (days)	**0 to 21**	**28 to 84**	**88 to 154**	**155 to 420**		

Table 5.16 Amyloid beta 42 outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments

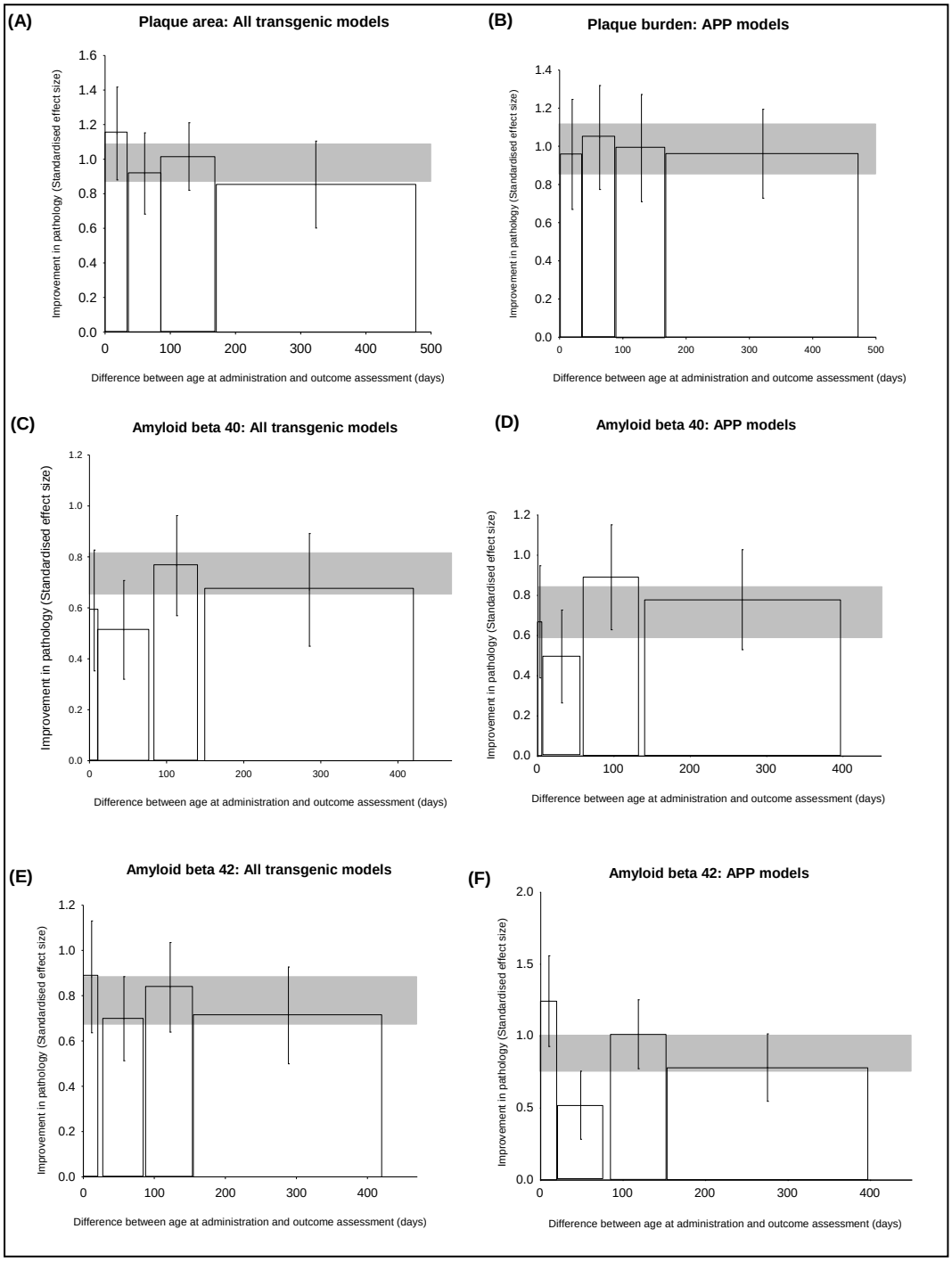


Figure 5.5: I stratified pathological outcomes according to the difference between the age at administration and assessment. Stratified summary estimates are given for tau, cellular infiltrates and neurodegeneration for all transgenic models (a, c, e) and for the most frequently used transgenic models (b,d,f). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

Tau

I stratified the 84 tau experiments into quartiles but this did not account for a significant proportion of the observed heterogeneity and the overall relationship was unclear (χ^2 =2.56, p<0.01, Figure 5.6) I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Tau and individual transgenic model groups

For both 3xTgAD and tau transgenic groups there were sufficient data for transgenic group specific analyses, however these did not account for a significant proportion of the observed heterogeneity (χ^2 =4.06 and χ^2= 4.1, Table 5.17).

	Quartiles				df=3 α=0.02	Critical χ^2 value
Tau	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
3xTgAD	1.01 (0.2 to 1.82) **12**	0.68 (0.22 to 1.14) **15**	0.62 (-0.03 to 1.28) **10**	0.34 (0.09 to 0.6) **11**	0.56 (0.32 to 0.81) **48**	**Non. sig.**
Quartiles (days)	3 to 15	28 to 84	112 to 168	173 to 419		
Tau	1.24 (0.37 to 2.12) **5**	0.41 (0.01 to 0.81) **6**	0.4 (0.13 to 0.67) **6**	1.03 (-0.2 to 2.27) **3**	0.63 (0.36 to 0.9) **20**	**Non. sig.**
Quartiles (days)	**28 to 65**	**84 only**	**112 to 168**	**196 to 252**		
Data overall	0.98 (0.53 to 1.43) 24	0.53 (0.24 to 0.83) 24	0.38 (-0.06 to 0.83) 14	0.37 (0.13 to 0.61) 22	0.55 (0.38 to 0.72) 84	**Non. sig.** (11.3 crit).
Quartiles (days)	3 to 28	30 to 84	94 to 150	168 to 419		

Table 5.17 Tau outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine 3xTgAD and tau transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments

Cellular infiltrates

I stratified the 87 cellular infiltrates experiments and identified that larger differences between the age at intervention administration and outcome assessment were associated with smaller estimates of effect size (χ^2 =98.2, Figure 5.6c). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Cellular infiltrates and individual transgenic model groups

For APP experiments I stratified data and identified an increase of cellular infiltrates where there were smaller differences between the age at administration intervention and outcome assessment (χ^2 =69.1, p<0.02, Figure 5.6d). For the APPPS1 group stratification by quartiles accounted for a significant proportion of the observed heterogeneity (χ^2 =29.5, p<0.02, Table 5.18). Estimates of efficacy did not suggest a clear relationship between the difference between age at administration and assessment and effect size.

	Quartiles				df=3 α=0.02	Critical χ^2 value
Amyloid beta 42	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	-0.27 (-0.96 to 0.43) **16**	0.82 (0.02 to 1.62) **16**	0.18 (-0.26 to 0.62) **14**	0.73 (-0.09 to 1.56) **14**	0.35 (-0.01 to 0.72) **60**	**Sig.**
Quartiles (days)	1 to 7	14 to 84	87 to 140	147 to 385		
APPPS	0.44 (-0.34 to 1.21) **7**	0.84 (0.52 to 1.17) **7**	-0.33 (-1.32 to 0.66) **6**	1.1 (-0.28 to 2.48) **5**	0.51 (0.02 to 0.99) **25**	**Sig.**
Quartiles (days)	3 to 55	63 to 84	105 to 140	168 to 420		
Data overall	-0.27 (-0.86 to 0.33) **22**	0.88 (0.41 to 1.34) **25**	0.02 (-0.41 to 0.44) **20**	0.87 (0.22 to 1.52) **20**	0.42 (0.13 to 0.7) **87**	**Sig.** (11.3 crit).
Quartiles (days)	1 to 21	28 to 84	87 to 140	147 to 420		

Table 5.18 (pervious page): Cellular infiltrate outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of

Neurodegeneration

For 62 neurodegeneration experiments I assessed the impact of the duration between the age at intervention administration and outcome assessment but this did not account for a significant proportion of the observed heterogeneity (χ^2 =8.61, Figure 5.6e). I inspected the dataset to identify whether there were sufficient experiments (≥20) for further exploration within each transgenic group.

Neurodegeneration and individual transgenic model groups

I stratified data in the APP transgenic model group, and identified that smaller differences between the age at intervention administration and outcome assessment were associated with higher estimates of effect size (χ^2 =22.1, p<0.02, Figure 5.6f)

	Quartiles				df=3 α=0.02	Critical χ^2 value
Neurodegen	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	1.41 (0.8 to 2.03) **11**	0.8 (0.08 to 1.53) **10**	0.65 (0.36 to 0.94) **16**	0.85 (0.46 to 1.24) **5**	0.84 (0.58 to 1.1) **42**	**Sig.**
Quartiles (days)	**3 to 90**	**92 to 154**	**168 only**	**177 to 294**		
Data overall	0.98 (0.47 to 1.48) **15**	1.41 (0.95 to 1.87) **16**	1.03 (0.2 to 1.86) **10**	0.70 (0.47 to 0.94) **21**	0.94 (0.72 to 1.15) **62**	**Non. Sig.** (11.3 crit).
Quartiles (days)	**3 to 28**	**35 to 92**	**112 to 154**	**168 to 321**		

Table 5.19 Neurodegeneration outcomes were stratified overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments

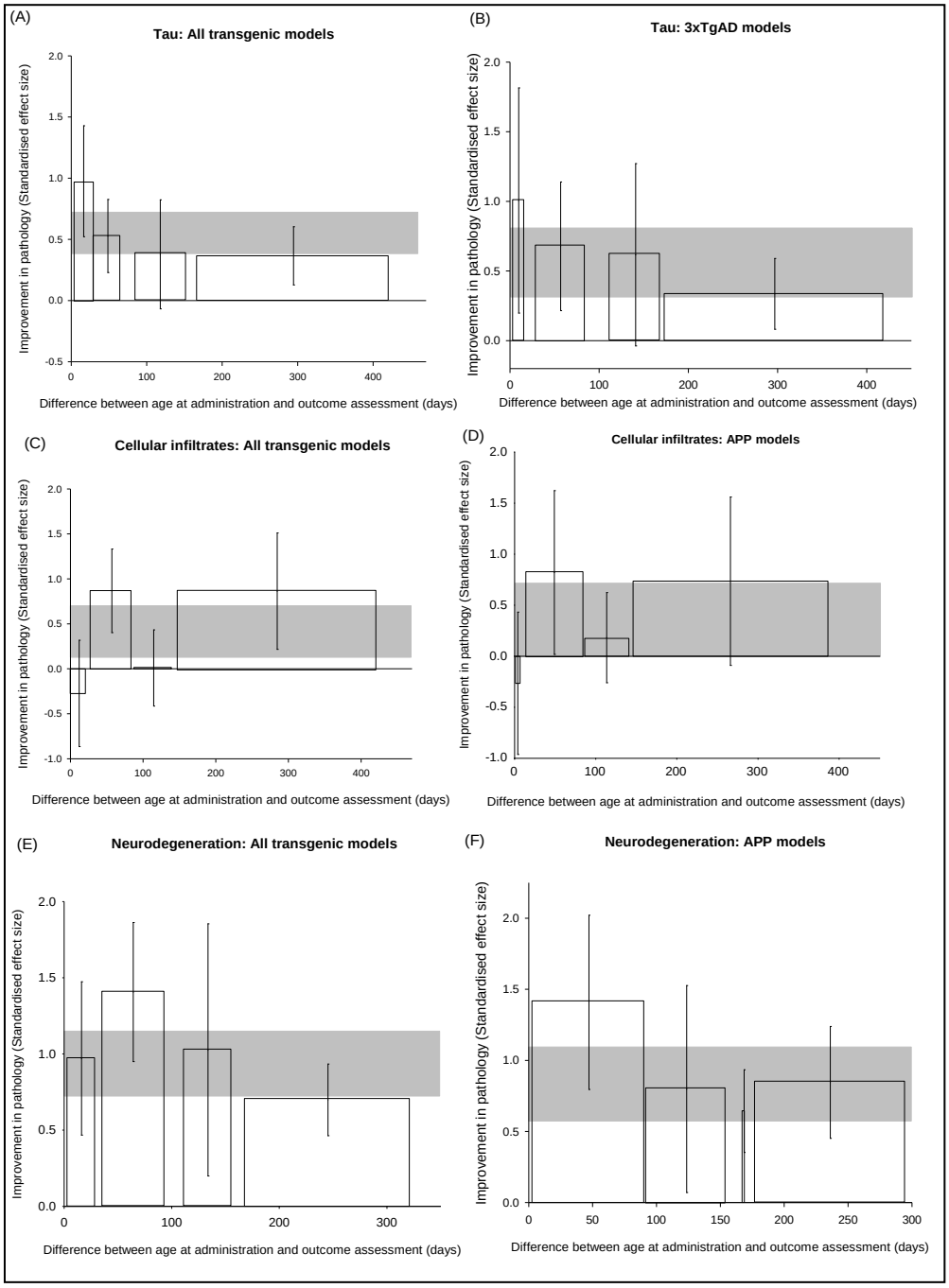


Figure 5.6: I stratified pathological outcomes according to the difference between the age at administration and assessment. Stratified summary estimates are given for each quartile for tau, cellular infiltrates and neurodegeneration for all transgenic models (a, c, e) and for the most frequently used transgenic models (b,d,f). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

5.2 Age specific analyses for neurobehavioural outcomes

For each outcome I stratify data into inter-quartile ranges to assess the impact of the age at intervention administration, outcome assessment, and the difference between intervention administration and outcome assessment. For age specific analyses, I stratify all data for a given outcome and then explore individual transgenic model groups separately wherever there are sufficient data to reflect differences in pathologies of the transgenic used. As I must stratify data into four categories, I took a conservative approach and stratify data wherever there were 20 or more experiments present within a single transgenic group. Table 5.20 describes the number of experiments performed across each of the main behavioural outcomes according to the transgenic group used. However, while sufficient data were present in order to investigate individual paradigms I envisaged that performing analyses on data overall would be more clinically relevant.

	Transgenic model group						
	APP	APPPS	3xTgAD	Tau	PS1	Other	Total
Acquisition phase	86	22	20	0	2	0	130
Probe phase	70	18	19	1	3	2	113
Other	67	40	10	3	1	2	123
Total	156*	56*	36*	3	4	4	259

Table 5.20: The number of experiments measuring different neurobehavioural outcomes according by transgenic model group. Where sufficient data were present for data overall (≥ 20 experiments) I stratified outcomes according to the transgenic model group used (shown by *).

5.2.1 Age at intervention administration

I first stratified neurobehavioral data overall to assess the impact age at intervention administration had on observed effect sizes which was possible for 256/259 experiments. Stratification accounted for a significant proportion of the observed heterogeneity where later ages of intervention administration were associated with higher estimates of efficacy (χ^2 =18.7, p<0.01, Figure 5.7a).

Neurobehaviour and individual transgenic model groups

Stratification by the age at administration did not account for a significant proportion of the observed heterogeneity for APP mice (χ^2 =2.10 Figure 5.7b) and clear relationships could not be identified with stratifying APPPS neurobehavioural outcomes (χ^2 =11.6, Table 5.21). Stratification of 3xTgAD outcomes suggested that higher estimates of efficacy were found at later ages of intervention administration (χ^2 =13.1, p<0.02, Table 5.21).

	Quartiles				df=3 α=0.02	Critical χ^2 value
NBS data	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	0.56 (0.38 to 0.74) **35**	0.64 (0.42 to 0.86) **35**	0.69 (0.52 to 0.85) **45**	0.81 (0.6 to 1.03) **40**	0.67 (0.57 to 0.76) **155**	**Non. Sig.**
Quartiles (days)	21 to 84	112 to 140	168 to 311	322 to 672		
APPPS	0.27 (-0.08 to 0.62) **12**	0.54 (0.32 to 0.76) **16**	0.45 (0.07 to 0.83) **11**	0.8 (0.45 to 1.14) **17**	0.54 (0.38 to 0.69) **56**	**Sig.**
Quartiles (days)	21 to 60	84 to 126	140 to 217	224 to 469		
3xTgAD	0.15 (-0.23 to 0.54) **9**	0.58 (0.29 to 0.87) **12**	0.89 (0.26 to 1.52) **4**	0.67 (0.21 to 1.14) **11**	0.55 (0.35 to 0.76) **36**	**Sig.**
Quartiles (days)	28 to 56	82 to 84	98 to 140	168 to 644		
Data overall	0.42 (0.26 to 0.59) **58**	0.61 (0.48 to 0.74) **75**	0.6 (0.44 to 0.77) **58**	0.82 (0.66 to 0.99) **65**	0.61 (0.54 to 0.69) **256**	**Sig. (10.8 crit).**
Quartiles (days)	**14 to 82**	**84 to 140**	**168 to 252**	**280 to 672**		

Table 5.21 (previous page): I stratified neurobehavioural outcomes according to the age at intervention administration overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

5.2.2 Age at outcome assessment

I first stratified neurobehavioral data overall to assess the impact age at outcome assessment had on observed effect size, which was possible for 255/259 experiments. Stratifying data overall, did not account for a significant proportion of the observed heterogeneity although I did observe that higher estimates of effect size were associated with later ages of outcome assessment (χ^2 =6.68, Figure 5.7c).

Neurobehaviour and individual transgenic model groups

APP transgenic models were the most commonly assessed transgenic model group (154 experiments) where estimates of efficacy were greater and later ages of assessment and this accounted for a significant proportion of the observed heterogeneity (χ^2 =13.2). Where I stratified APPPS transgenic experiments, data did not suggest a direction of effect and for 3xTgAD stratification did not account for a significant proportion of heterogeneity χ^2 =13.4 and χ^2 =9.59 respectively).

	Quartiles				df=3 α=0.02	Critical χ^2 value
NBS data	**Q1**	**Q2**	**Q3**	**Q4**	**All quartiles**	**10.2**
APP	0.43 (0.27 to 0.58) **40**	0.71 (0.55 to 0.88) **38**	0.78 (0.55 to 1.02) **38**	0.79 (0.58 to 1) **38**	0.67 (0.58 to 0.77) **154**	**Sig.**
Quartiles (days)	56 to 172	173 to 315	332 to 445	448 to 721		
APPPS	0.74 (0.53 to 0.95) **14**	0.37 (0.01 to 0.73) **14**	0.56 (0.23 to 0.89) **13**	0.46 (0.13 to 0.8) **15**	0.54 (0.38 to 0.69) **56**	**Sig.**
Quartiles (days)	84 to 224	227 to 268	280 to 322	336 to 547		
3xTgAD	0.31 (-0.11 to 0.74) **9**	0.59 (0.23 to 0.95) **9**	0.72 (0.43 to 1.01) **9**	0.58 (0.02 to 1.14) **9**	0.55 (0.35 to 0.76) **36**	**Non Sig.**
Quartiles (days)	117 to 201	230 to 345	421 to 486	508 to 656		
Data overall	0.48 (0.36 to 0.6) **66**	0.61 (0.45 to 0.77) **62**	0.7 (0.54 to 0.86) **63**	0.69 (0.52 to 0.86) **64**	0.62 (0.54 to 0.69) 255	**Non.Sig. (10.8 crit).**
Quartiles (days)	**35 to 196**	**197 to 313**	**314 to 434**	**444 to 721**		

Table 5.22 I stratified neurobehavioural outcomes according to the age at outcome assessment overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

5.2.3 Difference between age at administration and age at assessment

I first stratified neurobehavioral data overall to assess the impact the difference between age at administration and age at assessment had on observed effect size. Overall, 255 experiments suggested longer durations between administration and assessment were associated with larger effect sizes, however this did not account for a significant proportion of observed heterogeneity(χ^2 =2.38, Figure 5.7).

Neurobehaviour and individual transgenic model groups

I stratified APP data where higher estimates of efficacy were associated with longer durations between intervention administration and outcome assessment (χ^2 =25.9). Stratifying APPPS experiments also accounted for a significant proportion of observed heterogeneity (χ^2 =34.6, p<0.02), however there was no clear trend present. For 3xTgAD mice, stratification of data did not account for a significant proportion of the observed heterogeneity (χ^2 =2.31).

	Quartiles				df=3 α=0.02	Critical χ^2 value
NBS data	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**10.2**
APP	0.58 (0.39 to 0.77) **42**	0.55 (0.37 to 0.72) **35**	0.56 (0.36 to 0.75) **38**	0.95 (0.77 to 1.14) **39**	0.67 (0.58 to 0.77) **154**	**Sig.**
Quartiles (days)	0 to 28	31 to 88	89 to 167	168 to 394		
APPPS	0.86 (0.64 to 1.09) **14**	0.45 (0.08 to 0.82) **15**	0.69 (0.41 to 0.96) **13**	0.11 (-0.16 to 0.39) **14**	0.54 (0.38 to 0.69) **56**	**Sig.**
Quartiles (days)	0 to 61	63 to 100	103to 172	183 to 388		
3xTgAD	0.4 (-0.03 to 0.84) **9**	0.75 (0.34 to 1.15) **10**	0.53 (0.19 to 0.86) **10**	0.43 (-0.19 to 1.05) **7**	0.55 (0.35 to 0.76) **36**	**Non sig.**
Quartiles (days)	12 to 84	112 to 173	177 to 398	402 to 452		
Data overall	0.61 (0.46 to 0.75) **64**	0.56 (0.42 to 0.71) **61**	0.65 (0.5 to 0.81) **67**	0.63 (0.46 to 0.8) **63**	0.62 (0.54 to 0.69) **255**	**Non Sig.** (10.8 crit).
Quartiles (days)	**0 to 33**	**35 to 111**	**112 to 172**	**172 to 452**		

Table 5.23: I stratified neurobehavioural outcomes according to the difference between age at administration and outcome assessment overall, and by specific transgenic model groups. Sufficient data were present to examine APP, APPPS and 3xTgAD transgenic groups in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

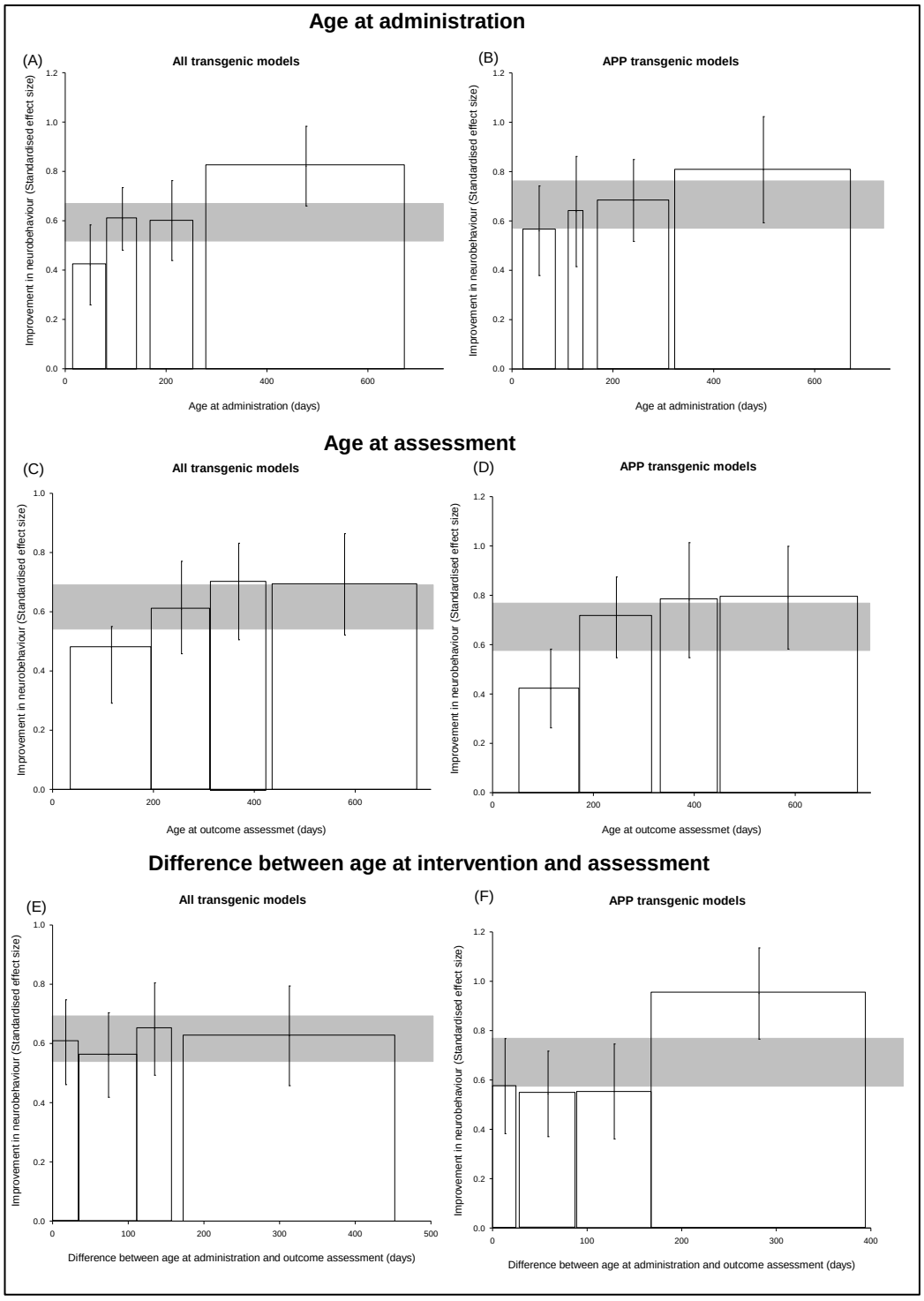


Figure 5.7: I stratified neurobehaviour outcomes according to the age at which interventions were administered (a,b), assessed (c,d) and the difference between the administration and assessment (e,f). Estimates are given overall and for the most commonly tested transgenic group (APP). Bar width represents extremes within each quartile, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

5.3 Sex analyses

5.3.1 Pathological outcome measures

I stratified the six pathological outcomes according to the sex of the animal used to identify whether data suggested an impact on observed outcomes (Table 5.24). For plaque burden I observed higher estimates for males opposed to females however this did not account for a significant proportion of the observed heterogeneity (χ^2 =11.0, Figure 5.8a). For amyloid beta 40 outcomes I observed moderately higher estimates of efficacy in males opposed to females (χ^2 = 10.4, Figure 5.8b) but this did not reach statistical significance. For amyloid beta 42, females were associated with higher estimates of efficacy (χ^2 =18.0 $p<0.01$, Figure 5.8c).

For tau, estimates of efficacy were higher in females opposed to males and this accounted for a significant proportion of the observed heterogeneity (χ^2 =46.7 $p<0.01$, Figure 5.8d). For outcomes regarding cellular infiltrates, I observed that male mice were associated with larger estimates than females (χ^2 =148, $p<0.01$, Figure 5.8e). Finally, neurodegeneration outcomes were greater in male mice than female mice but this did not account for a significant proportion of the observed heterogeneity (χ^2 =7.0, Figure 5.8f).

	Female SMD effect size (95 % CI) and N	Male SMD effect size (95 % CI) and N	Both SMD effect size (95 % CI) and N	Unknown SMD effect size (95 % CI) and N	Total SMD effect size (95 % CI) and N	Critical χ^2 value 11.3 df=3
Plaque area	0.65 (0.34 to 0.95) **48**	0.85 (0.42 to 1.28) **40**	1.05 (0.77 to 1.32) **83**	1.07 (0.93 to 1.21) **207**	0.98 (0.87 to 1.1) **378**	**Non. Sig.**
Amyloid beta 40	0.47 (0.28 to 0.67) **74**	0.51 (0.20 to 0.81) **53**	0.56 (0.34 to 0.77) **97**	0.96 (0.78 to 1.14) **164**	0.68 (0.57 to 0.79) **388**	**Non. Sig .**
Amyloid beta 42	0.67 (0.44 to 0.9) **74**	0.55 (0.23 to 0.87) **48**	0.53 (0.34 to 0.72) **76**	1.03 (0.87 to 1.2) **191**	0.78 (0.67 to 0.88) **389**	**Sig.**
Tau	0.48 (0.27 to 0.7) **7**	0.29 (-0.21 to 0.8) **7**	0.96 (0.63 to 1.29) **35**	0.28 (0.04 to 0.53) **35**	0.55 (0.38 to 0.72) **84**	**Sig.**
Cellular infiltrates	1.23 (0.15 to 2.31) **7**	2.39 (0.62 to 4.17) **4**	0.93 (0.27 to 1.59) **16**	0.04 (-0.24 to 0.33) **62**	0.4 (0.13 to 0.68) **89**	**Sig**
Neuro-degeneration	0.31 (-0.27 to 0.9) **2**	0.84 (0.29 to 1.38) **4**	0.92 (0.39 to 1.46) **18**	0.97 (0.73 to 1.22) **40**	0.91 (0.69 to 1.12) **64**	**Non.Sig.**

Table 5.24: I stratified each pathological outcome according to sex of the animal used. Estimates are given in terms of standardised effect size, brackets represent 95% confidence limits and N provides the number of experiments

5.3.2 Neurobehavioural outcome measures

259 neurobehavioural experiments suggested an overall improvement of 0.59 SD ([0.60 to 0.77], Table 5.25). Stratifying experiments according to the sex used accounted for a significant proportion of the observed heterogeneity ($\chi^2 = 25.4$, $p<0.02$, Figure 5.9) where female mice were associated with larger estimates of effect opposed to males, 0.79 SD (0.62 to 0.97, [38 experiments]) vs. 0.53 SD (0.35 to 0.70, [53 experiments]). For the 79 experiments performed where both sexes were used there was an estimated effect of 0.41 SD (0.28 to 0.50). For the 89 experiments performed where the sex was unclear the overall effect was 0.76 SD (0.63 to 0.89).

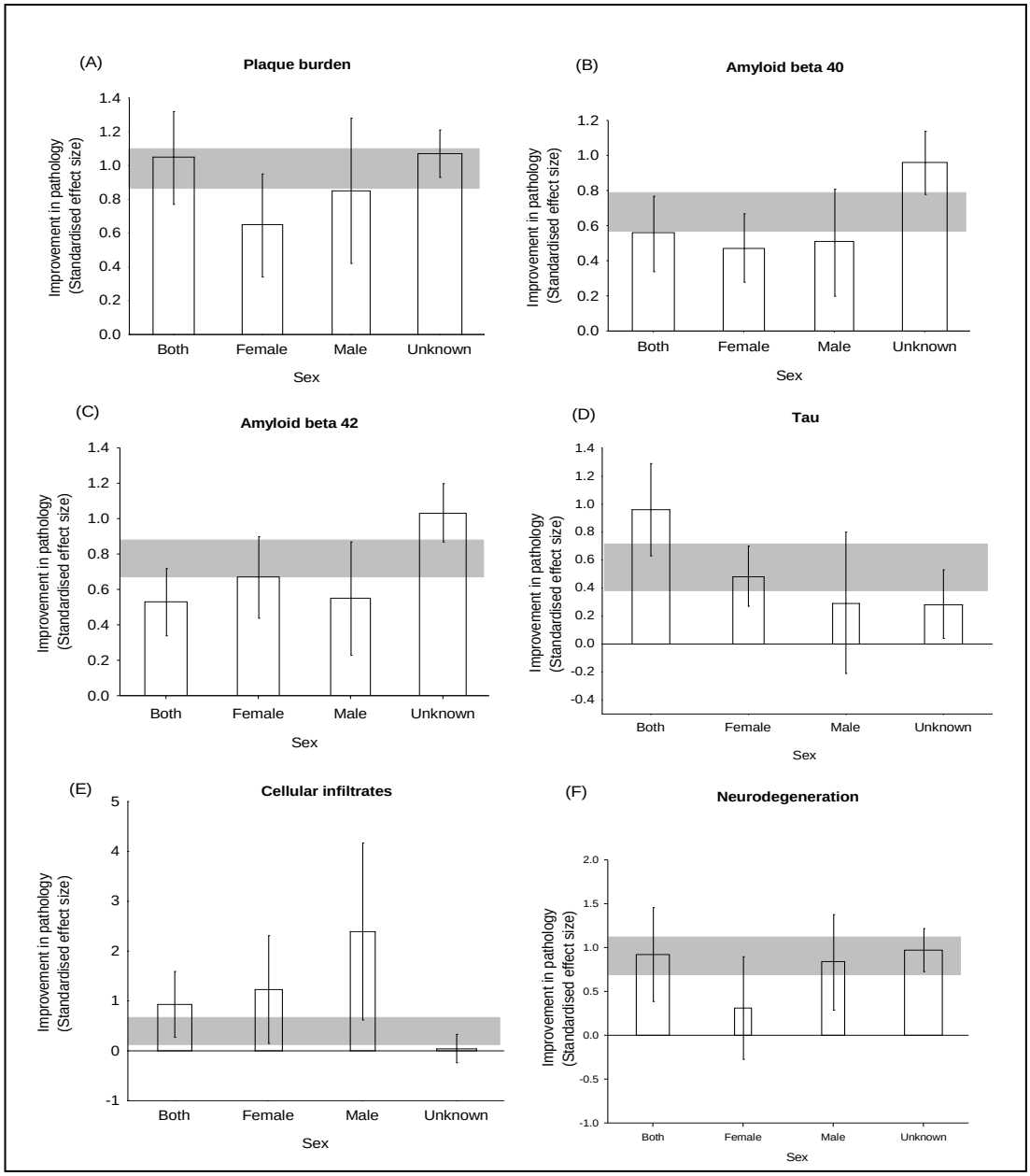


Figure 5.8: I stratified each pathological outcome (A) plaque burden, (B) amyloid beta 40, (C) amyloid beta 42, (D) Tau, (E) Cellular infiltrates and (F) neurodegeneration according to sex of the animal used. Bar width represents the log of the number of animals, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

Female SMD effect size (95 % CI) and N	Male SMD effect size (95 % CI) and N	Both SMD effect size (95 % CI) and N	Unknown SMD effect size (95 % CI) and N	Overall SMD effect size (95 % CI) and N	Critical χ^2 value 10.8 df= 4
0.79 (0.62 to 0.97) **38**	0.53 (0.35 to 0.70) **53**	0.41 (0.28 to 0.54) **79**	0.76 (0.63 to 0.89) **89**	0.69 (0.6 to 0.77) **259**	**25.4 Sig.**

Table 5.25: I stratified neurobehavioural outcomes according to sex of the animal used. Estimates are given in terms of standardised effect size, brackets represent 95% confidence limits and N provides the number of experiments.

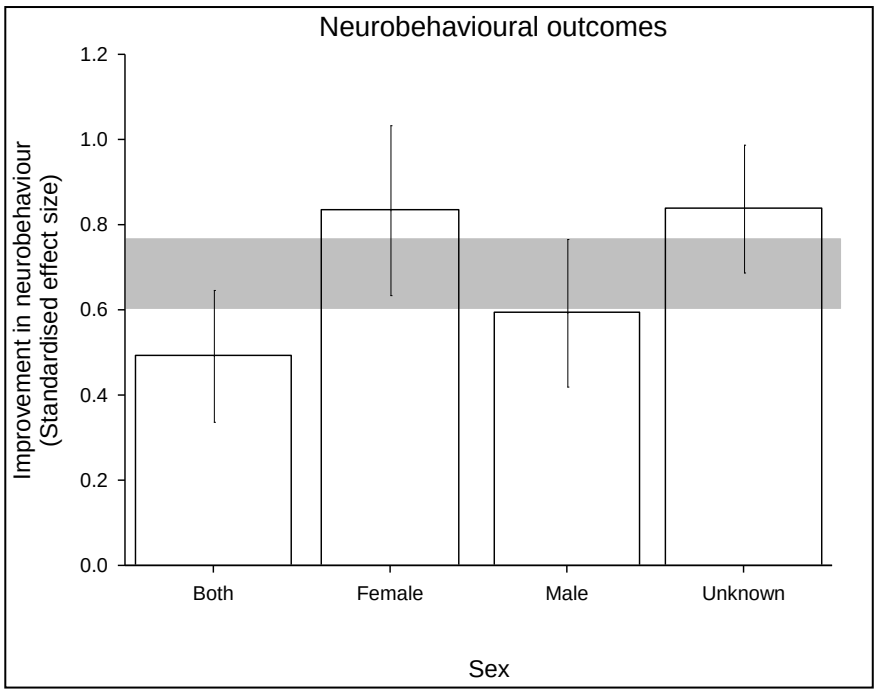


Figure 5.9: I stratified neurobehavioual outcome according to sex of the animal used. Bar width represents the log of the number of animals, error bars represent 95 % confidence limits and grey bar denotes 95% confidence limit of global estimate.

5.4 Defining the transgenic model

To add greater depth to our analyses where interventions were tested I identified the impact of the transgene itself on pathology and neurobehaviour within control transgenic mice. Datasets used for this approach were not considered comprehensive as they have not been identified through a systematic approach. Without this approach it is not possible to determine how much of published data analyses represent (Figure 5.10). Nevertheless analyses are useful in the respect that they represent those control transgenic animal s used within analyses described and are thus relevant in order to further understand relationships.

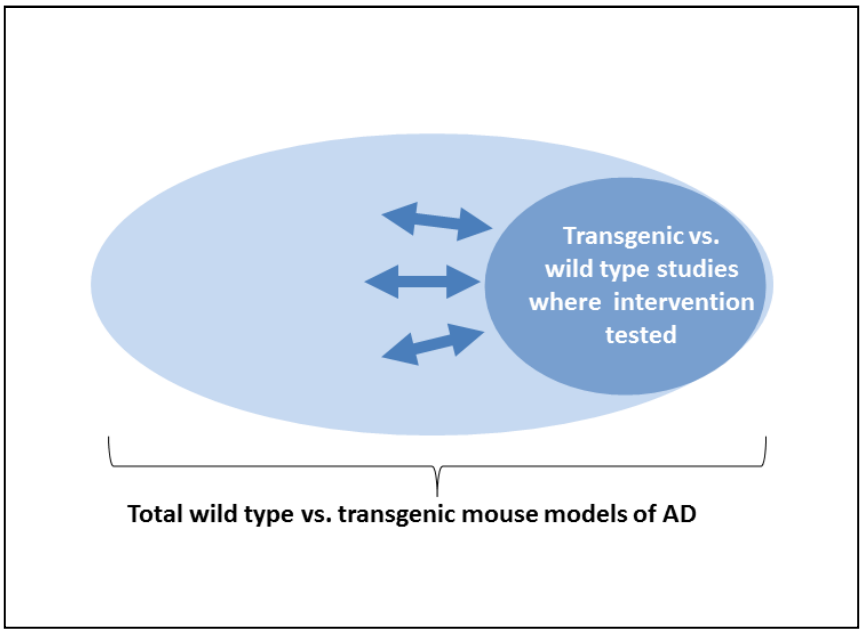


Figure 5.10: I conducted analyses to improve our understanding of transgenic models used in analyses. Such models represent an unknown proportion of all available literature but their utility is that such data represents those transgenic models used in analyses conducted.

5.4.1 Calculating effect sizes to assess the impact of transgenes

I first required an estimate of effect in order to assess the impact of transgenes. For pathological experiments, the reporting of wild type behaviour was relatively rare (<5%), and as I could not impute wild type behaviour this restricted the use of SMD to calculated effect sizes. As alternative I used z scores to calculate pathological effect sizes, by taking the mean value in the control divided by the calculated standard deviation. For neurobehavioural outcomes, 185 of the 259 experiments (71.4%) of experiments reported wild type performance and thus I could use SMD calculations of effect size for meta-analyses.

	Pathological outcomes	Neurobehavioural outcomes
Percentage of experimental cohorts where wild type data are reported	**<5%**	71.4%
For assessing the impact of the transgene I calculate effect sizes using:	**Z scores**	**Standardised mean difference**
Percentage of total dataset contributing to estimates	**100%**	71.4%

Table 5.24 I estimated the impact of the transgene through different methods for pathology (z-scores) and behaviour (Standardised mean difference) reflecting differences in the reporting of wild type animals.

5.4.2 Defining the pathological burden within transgenic models

I first summarised the number of studies where there was a comparison between transgenic and wild type mice. Sufficient data (≥ 20 experiments) were present to investigate outcomes overall, and for a number of outcomes within specific transgenic model groups (Table 5.8). As our analyses were focused specifically on the transgenic models, I was conscious to take into account differences in the extent and severity of pathologies across different transgenes. Therefore, I chose to only perform analyses within transgenic model groups.

	Plaque burden	Amyloid beta 40	Amyloid beta 42	Tau	Cellular infiltrates	Neurodegeneration
APP	172*	164*	171*	5	45*	27*
APPPS	66*	47*	53*	3	20*	10
3xTgAD	18	22*	20*	35*	1	1
Tau	0	1	1	14	2	6
PS1	0	1	1	0	0	0
Other	4	0	1	4	0	0
All data	**260**	**235**	**247**	**61**	**68**	**44**

Table 5.25: The number of experiments which compare transgenic performance with wild type performance across each pathological outcome and overall. Where there were ≥ 20 experiments data could be taken forward to age specific analyses (*).

Plaque burden

For outcomes regarding plaque burden, there were sufficient data to investigate the impact of age at outcome assessment for both APP and APPPS groups (Table 5.25). For APP models I estimated an overall effect of the transgene on plaque pathology of 3.72 (3.09 to 4.35). Stratifying 170 APP experiments using those quartiles defined where interventions were tested did not suggest a particular direction of effect (χ^2 =25.1, p<0.05, 170 comparisons,).

For the APPPS transgenic group, 66 experiments suggested a stronger impact of the transgene on plaque pathology, with an overall z score effect of 7.28 (3.51 to 11.05). Where I stratified data according to the age at outcome assessment I found higher estimates of efficacy at later ages of outcome assessment (χ^2 =834, p<0.05, 66 comparisons, Table 5.26).

	Quartiles				df=3 α=0.05	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	3.84
APP	3.95 (3 to 4.91) **37**	3.54 (2.1 to 4.98) **43**	3.58 (2.48 to 4.69) **45**	3.82 (2.71 to 4.93) **45**	3.72 (3.09 to 4.35) **170**	**Sig.**
Quartiles (days)	66 to 231	252 to 364	368 to 469	476 to 721		
APPPS	3.17 (2.07 to 4.26) **19**	4.19 (2.37 to 6.02) **12**	13.99 (-0.36 to 28.33) **17**	7.42 (2.96 to 11.90) **18**	7.28 (2.06 to 12.5) **66**	**Sig.**
Quartiles (days)	65 to 210	211 to 252	266 to 336	364 to 560		

Table 5.26: I stratified plaque burden outcomes according to the age at outcome assessment to assess the impact of the transgene. Sufficient data were present to examine APP and APPPS transgenic groups in further detail. Estimates of efficacy are given in z scores, brackets give 95% CI and with number of experiments.

Amyloid beta 40

For amyloid beta 40 outcomes there were sufficient data to examine APP, APPPS and 3xTgAD in further detail (Table 5.27). 161 APP experiments suggested a z score impact of 6.18 (5.04 to 7.33). I observed an inverse association between the age of outcome assessment and transgene effect (χ^2 =593, p<0.05, Table 5.27).

For APPPS transgenic models , 47 experiments suggested the overall impact of amyloid beta 40 was 3.67 (3.02 to 4.31). Where I stratified data according to the age at assessment I identified smaller extents of amyloid beta 40 were associated with later ages of assessment (χ^2 =34.5 , p<0.05, Table 5.27). For 3xTgAD, 22 experiments suggested an overall effect of 3.18 (1.74 to 4.63). Where I stratified such data I identified an inverse relationship between age and the degree of amyloid beta 40 pathology (χ^2 =72.1, p<0.05, Table 5.27).

	Quartiles				df=3 α=0.05	Critical χ^2 value
	Q1	**Q2**	**Q3**	**Q4**	All quartiles	**3.84**
APP	8.33 (5.10 to 11.56) 20	7.50 (4.83 to 10.2) 46	6.59 (4.21 to 8.98) 47	3.62 (2.46 to 4.30) 48	6.18 (5.04 to 7.33) 161	**Sig.**
Quartiles (days)	51 to 113	115 to 290	308 to 406	413 to 714		
APPPS	5.14 (3.25 to 7.03) **10**	3.25 (2.00 to 4.50) **12**	3.94 (2.88 to 4.99) **11**	2.74 (1.86 to 3.61) **14**	3.67 (3.02 to 4.31) **47**	**Sig.**
Quartiles (days)	56 to 112	120 to 210	224 to 300	301 to 672		
3xTgAD	4.33 (-1.30 to 9.96) **5**	3.82 (2.43 to 5.21) **5**	2.66 (1.20 to 4.13) **6**	2.28 (1.69 to 2.87) **6**	3.18 (1.74 to 4.63) **22**	**Sig.**
Quartiles (days)	112 to 168	210 to 289	336 to 448	450 to 672		

Table 5.27: I stratified amyloid beta 40 outcomes according to the age at outcome assessment to assess the impact of the transgene. Sufficient data were present to examine APP and APPPS transgenic groups in further detail. Estimates of efficacy are given in z scores, brackets give 95% CI and with number of experiments.

Amyloid beta 42

For amyloid beta 42 outcomes there were sufficient data to examine APP, APPPS and 3xTgAD in further detail (Table 5.28). 169 APP experiments suggested a z score impact of 5.67 (4.55 to 6.79). I stratified data and identified that later ages of outcome assessment were associated with lower estimates of impact (χ^2 =173, p<0.05, Table 5.28).

Overall I estimated the amyloid beta 42 impact within APPPS transgenes at 4.50 (3.51 to 5.49) from 53 experiments. Where I stratified APPPS data according to the age at outcome assessment I found this accounted for a significant proportion of the observed heterogeneity the overall relationship remained unclear (χ^2 =73.0, p<0.05, Table 5.28). For 20 3xTgAD experiments the overall impact was 3.76 (2.69 to 4.84) and stratification suggested an inverse relationship between age at outcome assessment and transgene effect (χ^2 =54.0, p<0.05, Table 5.28).

	Quartiles				df=3 α=0.05	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	3.84
APP	6.86 (4.55 to 9.18) **31**	6.66 (3.15 to 10.17) **45**	5.15 (3.90 to 6.40) **51**	4.35 (3.29 to 5.40) **42**	5.67 (4.63 to 6.71) **169**	**Sig.**
Quartiles (days)	42 to 141	142 to 308	317 to 413	420 to 714		
APPPS	4.02 (2.70 to 5.35) **11**	5.97 (3.19 to 8.74) **15**	4.95 (2.89 to 7.01) **12**	2.99 (2.11 to 3.88) **15**	4.50 (3.51 to 5.49) **53**	**Sig.**
Quartiles (days)	56 to 112	120 to 224	231 to 300	301 to 627		
3xTgAD	5.72 (2.37 to 9.07) **5**	4.45 (2.09 to 6.82) **3**	3.38 (2.01 to 4.76) **2**	2.25 (1.66 to 2.84) **10**	3.76 (2.69 to 4.84) **20**	**Sig.**
Quartiles (days)	112 to 168	210 to 252	336 to 448	450 to 672		

Table 5.28 (previous page): I stratified amyloid beta 42 outcomes according to the age at outcome assessment to assess the impact of the transgene. Sufficient data were present to examine APP and APPPS transgenic groups in further detail. Estimates of efficacy are given in z scores, brackets give 95% CI and with number of experiments.

Tau

35 experiments reported tau outcomes within the 3xTgAD group and overall, the z-score estimated impact was 8.77 (5.72 to 11.82) where there was considerable heterogeneity present (χ^2 =9913). When I stratified data according to the age at outcome assessment I found that this accounted for a significant proportion of the observed heterogeneity but the overall relationship was unclear (Table 5.29, χ^2 =3579, p<0.05, Table 5.29).

	Quartiles				df=3 α=0.05	Critical χ^2 value
	Q1	**Q2**	**Q3**	**Q4**	All quartiles	**3.84**
3xTgAD	6.23 (2.95 to 9.51) **10**	4.31 (2.17 to 6.44) **6**	20.04 (8.26 to 31.83) **9**	3.79 (2.38 to 5.2) **10**	8.77 (5.72 to 11.82) **35**	**Sig.**
Quartiles (days)	120 to 231	252 to 336	339 to 381	420 to 672		

Table 5.29: I stratified tau outcomes according to the age at outcome assessment to assess the impact of the transgene. Sufficient data were present to examine the 3xTgAD in further detail. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

Cellular infiltrates

44 cellular infiltrate experiments were reported from the APP transgenic group and I estimated an overall z score effect size of 4.53 (3.59 to 5.46). I stratified data according to the age at outcome assessment and found that this explained a

significant proportion of the observed heterogeneity, although it was difficult to determine relationships (χ^2 =218, p<0.05, Table 5.30).

	Quartiles				df=3 α=0.05	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	3.84
APP	5.13 (3.34 to 6.92) **13**	4.68 (3.31 to 6.05) **10**	2.89 (1.79 to 3.98) **12**	5.67 (2.91 to 8.42) **9**	4.53 (3.59 to 5.46) **44**	**Sig.**
Quartiles (days)	112 to 287	308 to 433	445 to 504	507 to 714		

Table 5.30: I stratified APP outcomes according to the age at outcome assessment to assess the impact of the transgene. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

Neurodegeneration

26 experiments were performed in APP transgenic mice which had an estimated overall effect of 4.89 (3.50 to 6.29). Stratifying data according to the age at outcome assessment explained a significant proportion of the observed heterogeneity (χ^2 =137, p<0.05, Table 5.31) where there was a moderate association between increasing effect size and age.

	Quartiles				df=3 α=0.05	Critical χ^2 value
	Q1	Q2	Q3	Q4	All quartiles	3.84
APP	5.57 (3.33 to 7.82) **10**	3.07 (1.49 to 4.66) **6**	4.24 (-0.22 to 8.7) **5**	6.41 (4.27 to 8.54) **5**	4.89 (3.5 to 6.29) **26**	**Sig.**
Quartiles (days)	112 to 252	260 to 364	371 to 493	504 to 630		

Table 5.31: I stratified neurodegeneration outcomes from APP control mice according to the age at outcome assessment to assess the impact of the transgene. Estimates of efficacy are given in standardised effect sizes, brackets give 95% CI and with number of experiments.

5.4.3 Defining the neurobehavioural deficits within transgenic models

Similar to pathological outcomes, I first summarised how many comparisons between wild type and transgenic cohorts (Table 5.32). Sufficient data were present within the APP (67 experiments), APPPS (40 experiments) and 3xTgAD (25 experiments in order to permit further analysis. In order to inform these analyses further, I plotted estimates of effect size according to the age at assessment as shown in Figure 5.11.

	Neurobehavioural outcomes
APP	67*
APPPS	40*
3xTgAD	25*
Tau	2
PS1	4
Other	2
All data	**140**

Table 5.32 I summarised the number of experiments which compare transgenic neurobehavioural performance with wild type performance overall and within each transgenic model group. Where there were >20 experiments data could be taken forward to age specific analyses(*).

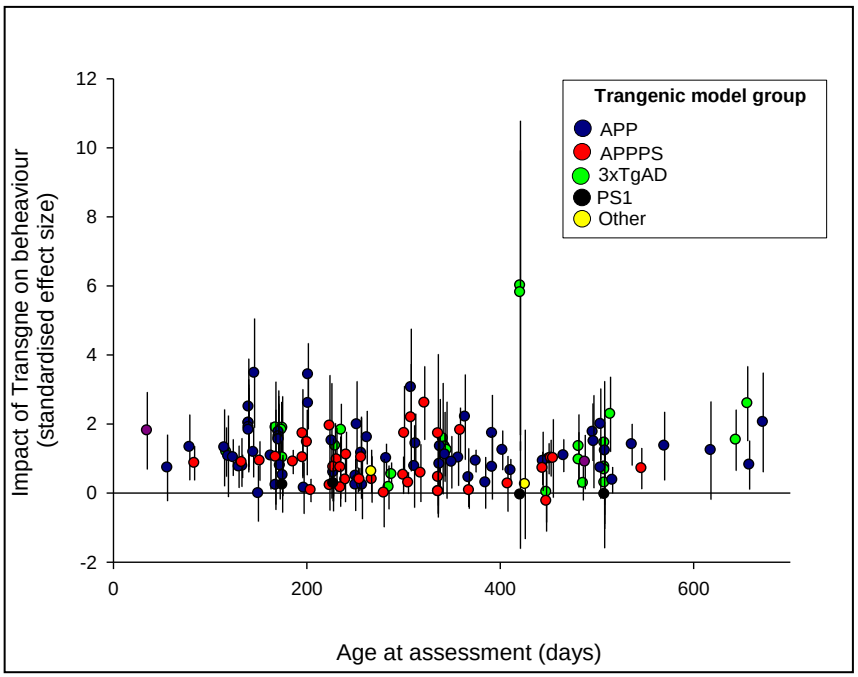


Figure 5.11: To illustrate the spread of the data I plotted the impact of the transgene (standardised effect size) against the age at outcome assessment (days) according to the transgenic group used

For APP experiments I took forward 66 experiments (therefore excluding 1 experiment) where I could identify the age at assessment and calculated an overall impact of 1.12 SD (0.97 to 1.27). Stratification of estimates by the age at outcome assessment did not prove significant (χ^2=3.17, p<0.05, Table 5.33). APPPS experiments suggested an overall impact of the transgene of 0.68 SD (0.51 to 0.84) and stratification proved statistically significant (χ^2=15.0, p<0.05, Table 5.33). For 3xTgAD models, I estimated an effect of 1.22 SD (0.90 to 1.53) and while stratification did account for a significant proportion of heterogeneity (χ^2=18.5, p<0.05, Table 5.33) this was not reflected by a relationship between transgene effect and age at outcome assessment.

					df=3 α=0.05	Critical χ^2 value
NBS data	**Q1**	**Q2**	**Q3**	**Q4**	All quartiles	**3.84**
APP	1.23 (0.95 to 1.51) **22**	1.15 (0.73 to 1.57) **17**	0.9 (0.72 to 1.09) **13**	1.14 (0.72 to 1.09) **14**	1.14 (0.86 to 1.41) **66**	**Non sig**
Quartiles (days)	56 to 172	173 to 315	332 to 445	448 to 721		
APPPS	0.94 (0.73 to 1.16) **7**	0.53 (0.29 to 0.77) **13**	0.85 (0.33 to 1.36) **8**	0.57 (0.23 to 0.91) **12**	0.68 (0.52 to 0.84) **40**	**Sig.**
Quartiles (days)	84 to 224	227 to 268	280 to 322	336 to 547		
3xTgAD	1.47 (1.09 to 1.86) **5**	1.04 (0.54 to 1.55) **7**	0.96 (0.14 to 1.78) **6**	1.46 (0.81 to 2.11) **7**	1.22 (0.9 to 1.53) **25**	**Sig**
Quartiles (days)	117 to 201	230 to 345	421 to 486	508 to 656		

Table 5.33: I summarise the number of experiments which compare transgenic neurobehavioural performance with wild type performance specific for each transgenic group and overall. Where there were >20 experiments data could be taken forward to age specific analyses.

5.4.4 Quantifying the impact of transgene, pathology and neurobehaviour

In order to establish whether sufficient data were present to explore potential relationships between pathology and neurobehaviour in transgenic control animals I summarised data were both outcomes were observed. Overall, I identified 82 experiments where I could estimate the effect of transgenic for both pathology and neurobehaviour. Where I performed meta-regression on such data I observed that changes in pathology could explain 11.0% of changes in neurobehaviour (Figure 5.12). More specifically I had sufficient data to investigate relationships within APP (43 experiments) and APPPS (28 experiments) transgenic model groups.

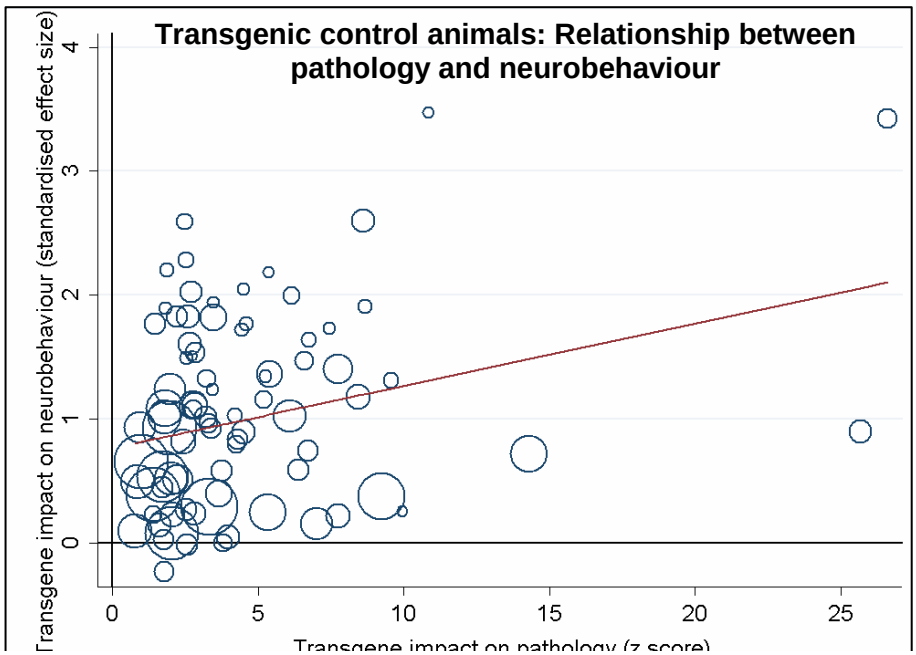


Figure 5.12: I performed meta-regression on the 82 experiments where I could estimate the impact of transgenes on pathology and neurobehaviour. Each symbol represents a single experiment and size denotes the inverse variance (and therefore weight in analysis).

Transgenic model group	Number of experiments
APP	43*
APPPS	28*
3xTgAD	9
Tau	1
PS1	0
Other	1
All data	**82**

Table 5.34: I summarised the number of experiments where I could estimate the impact of transgenes on neurobehaviour and pathology overall, and within specific transgenic groups. Where there were >20 experiments data could be taken forward to age specific analyses.

Where I examined APP mice, I identified a strong positive correlation between changes in pathology and neurobehaviour, while I also observed a correlation between changes observed in APPPS mice, this did not prove statistically significant (Figure 5.13 and Table 5.35).

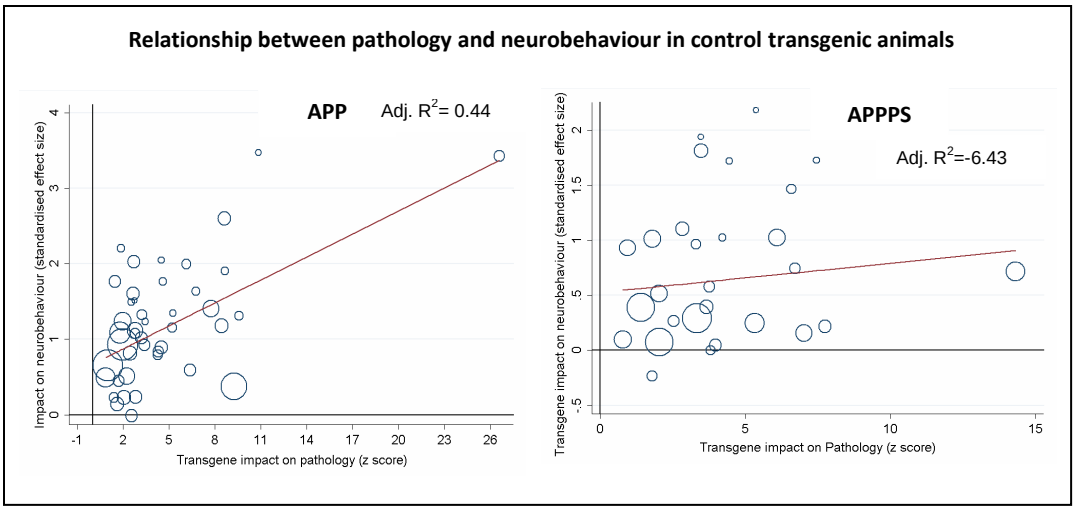


Figure 5.13 (previous): I performed meta-regression on the both APP and APPPS transgenic mice where I could estimate the impact of transgenes on pathology and neurobehaviour. Each symbol represents a single experiment and size denotes the inverse variance (and therefore weight in analysis).

	Co-efficient (SMD ES)	Standard error	τ	P>|t|	Lower 95% CI	Upper 95 CI%	N	Adj. R^2
Changes in pathology vs. NB across all transgenic models	0.05	0.018	2.77	0.007	0.014	0.087	**82**	0.11
Changes in pathology vs. NB in APP transgenic models	0.101	0.023	4.5	0	0.056	0.147	**43**	0.44
Changes in pathological vs. NB in APPPS transgenic models	0.027	0.036	0.73	0.472	-0.048	0.102	**28**	-6.43

Table 5.35: Meta-regression comparing probe phase with acquisition curves, first and last time point of acquisition curve and sections in-between. For each comparison co-efficient is given, standard error, tau (τ), significance level, 95% confidence limits, number of experiments (N) and Adjusted R^2 (Adj. R^2)

5.5 Interpreting transgenic model analyses

5.5.1 Summary of findings

Within this chapter, analyses identified a number of associations between age and intervention effect, however interpretation must be made cautiously as there were few common trends that proved statistically significant.

For amyloid related outcomes (plaque burden, amyloid beta 40 and 42) I found smaller effect sizes associated with later ages of administration and assessment (i.e. APP and APPPS mice) suggesting that early intervention could improve observed outcomes. Where I assessed age of assessment on the pathological impact of the transgene, data suggested that the extent of amyloid beta 40 and 42 lessens over time whereas plaque burden becomes more extensive.

For tau, the overall relationship between the age of animals and intervention effect was unclear at the overall level and at the transgenic model group level. Further, where I assessed control mice for the impact of the transgene there was no specific associations identified. For cellular infiltrates perhaps the most interesting result was regarding the age at outcome assessment, where later ages were associated with smaller effects for (data overall and within the APP group). However, no specific relationships were suggested within our transgene analysis.

For neurodegeneration outcomes intervention analyses did not suggest a particular direction of effect, but where I inspected the impact of the transgene there was a modest increase in the severity for APP mice at later ages of assessment.

For sex analyses, males had higher estimates of efficacy for four out of six pathological outcomes but these were frequently marginal, and there was consistent overlapping of 95% confidence limits with female mice. Perhaps a more notable concern was that 50% (699/1392) of experiments did not state the sex of the animal used. For neurobehavioural outcomes female transgenic mice were associated with greater improvements than males however where both males and females were assessed estimated of effect were considerably smaller, which weakens the strength of this hypothesis.

Across age related analyses it is a consideration that the age at outcome assessment, duration of treatment or length of follow up may not be entirely independent variables. For example the length of treatment possible will be at times determined by how long the animal lives (i.e. the age at outcome assessment).Thus the interdependency between age at outcome assessment and length of treatment means suggested associations must be interpreted with caution.

5.5.2 Implications of findings

Stratifying data into inter-quartile ranges did not identify many definitive relationships, and where relationships were observed these were frequently specific to individual transgenic model groups. Nonetheless, there were a number of outcomes where increasing age was associated with difference in effect size (such as neurodegeneration and age at intervention administration). Therefore such differences reiterate the need for experiments to be performed most reflective of the clinical conditions in which it is proposed they will be tested.

The lack of reporting of the sex of the animals used in these studies is concerning considering that numerous differences have been identified between different transgenic lines. While this limits the statistical power of our analyses to identify differences I did find differences between the sex used. Therefore the empirical data suggest that identifying (and reporting) efficacy across both male and female mice may improve the external validity of findings.

Where I examined the impact of transgenes on pathology there was a suggestion that the shift in amyloid over time results in a decrease of amyloid species at the same time that plaque burden increases. While this offers a hypothesis of model development it is not conclusive. Perhaps the most interesting finding is that variation in pathology can only explain 11% of variation in neurobehaviour. This value is smaller than the changes observed where interventions are tested. While a greater dataset would provide a statistically more powerful analysis I have demonstrated the feasibility of this approach.

Chapter 6 Intervention specific analyses

Each of the publications included in this review performed experiments to ascertain the impact of a given intervention within transgenic models of Alzheimer's disease. From the 427 publications, 357 individual intervention strategies were described and I provide estimates of efficacy across pathology and behaviour. Overall, I identified 273 interventions which assessed changes in pathological outcomes, whereas 107 interventions assessed changes in neurobehaviour. I estimated that 24 % (84/357) of interventions were assessed in more than one transgenic model.

To improve our understanding of data regarding individual interventions, where outcomes are reported from the most frequently reported interventions (> 5 publications), I summarised these in greater detail. Additionally, where data permit I inspect individual interventions and intervention groups.

6.1 Interventions reported in 5 or more publications

There were 16 interventions reported in five or more publications and I derived estimates of efficacy for each of the pathological outcomes; plaque burden, amyloid beta 40, amyloid beta 42, tau, cellular infiltrates and neurodegeneration (Table 6.1). I also summarise data regarding neurobehavioural outcomes where I describe analyses for neurobehaviour overall, and for the acquisition and probe phase of the MWM alongside other behavioural paradigms used.

Pathological outcomes

6.1.1 Plaque burden

Within the 16 most commonly reported interventions, all 16 assessed changes in plaque burden (Table 6.1). Antibody 3d6 was associated with larger estimates of effect size where two experiments suggested a reduction of 2.24 SD (1.14 to 3.33) The one study which assessed the impact of aluminium suggested a worsening of outcome with an effect size of -1.27 SD (-2.07 to -0.47). Across all interventions and outcomes tested, the assessment of plaque burden after treatment with amyloid beta 42 was the most commonly reported (42 experiments).

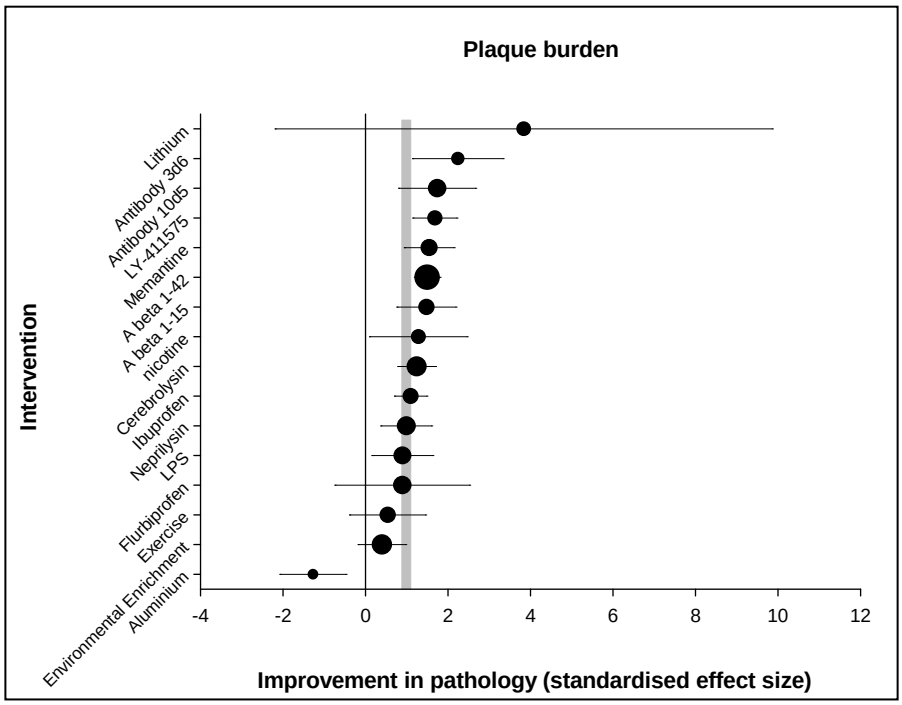


Figure 6.1: Interventions examined in five or more publications are stratified according to plaque burden estimates of effect size. Error bars represent 95% confidence limits and grey bar represents the 95% confidence limit across all interventions, symbol size represents the log of the number of animals. Grey bar represents 95% CI across all interventions

6.1.2 Amyloid beta 40

Within the 16 most commonly reported interventions, 15 assessed changes in amyloid beta 40 (Figure 6.2). Of 22 LY-411575 experiments, all 22 examined changes in amyloid beta 40 levels. Such studies were associated with the largest effect size within this group and amyloid beta 40 was reduced by 2.15 SD (1.43 to 2.87). Conversely, the use of lipopolysaccharide (LPS) was associated with a worsening of amyloid beta 40 by an estimated -0.48 SD (-1.19 to 0.23).

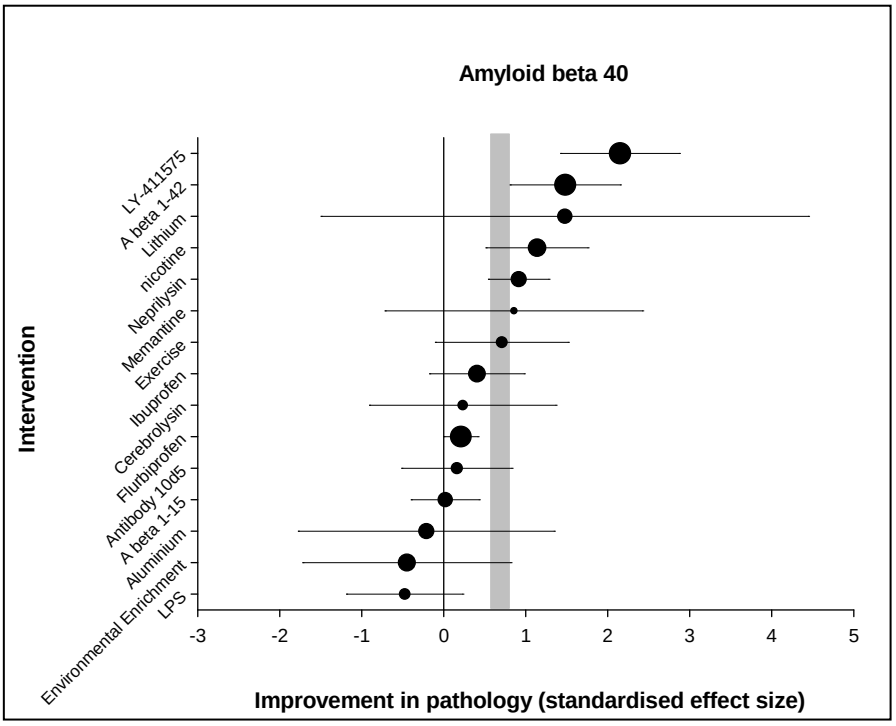


Figure 6.2: Interventions which were examined in five or more publications are stratified according to amyloid beta 40 estimates of effect size. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Grey bar represents 95% CI across all interventions

6.1.3 Amyloid beta 42

Interestingly, while all 22 LY-411575 experiments assessed amyloid beta 40 levels only 9 experiments estimated the effect on amyloid beta 42 where there was an overall improvement of 1.67 SD (0.78 to 2.56). Significantly higher estimates of efficacy were associated with the use of lithium, which was reduced amyloid beta 42 by 5.40 SD (2.84 to 7.95). In accordance with changes in amyloid beta 40, LPS was associated with an increase in amyloid beta 42 (-0.32 SD [-1.02 to 0.38], 1 experiment).

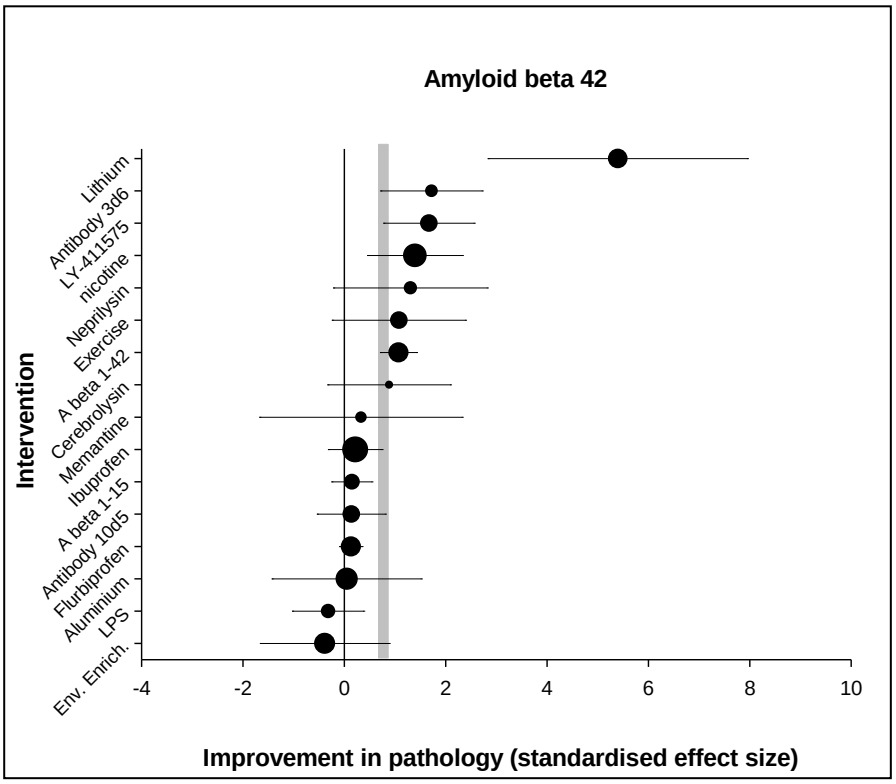


Figure 6.3: Interventions which were examined in five or more publications are stratified according to amyloid beta 42 estimates of effect size. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Grey bar represents 95% CI across all interventions

6.1.4 Tau

Seven of the 16 most commonly reported interventions reported tau outcomes however data were limited (mode 1, Table 6.1). Of the seven interventions, only lithium and ibuprofen were associated with an improvement of tau pathologies. Higher estimates of efficacy were associated with lithium where 9 experiments suggested a reduction the extent of tau pathology by an estimated 0.97 SD (0.51 to 1.42). Neprilysin and LPS both suggested a worsening of outcome and although data were limited (1 experiment for each), nicotine also suggested a worsening of outcome (-1.39 SD [-2.42 to -0.35]).

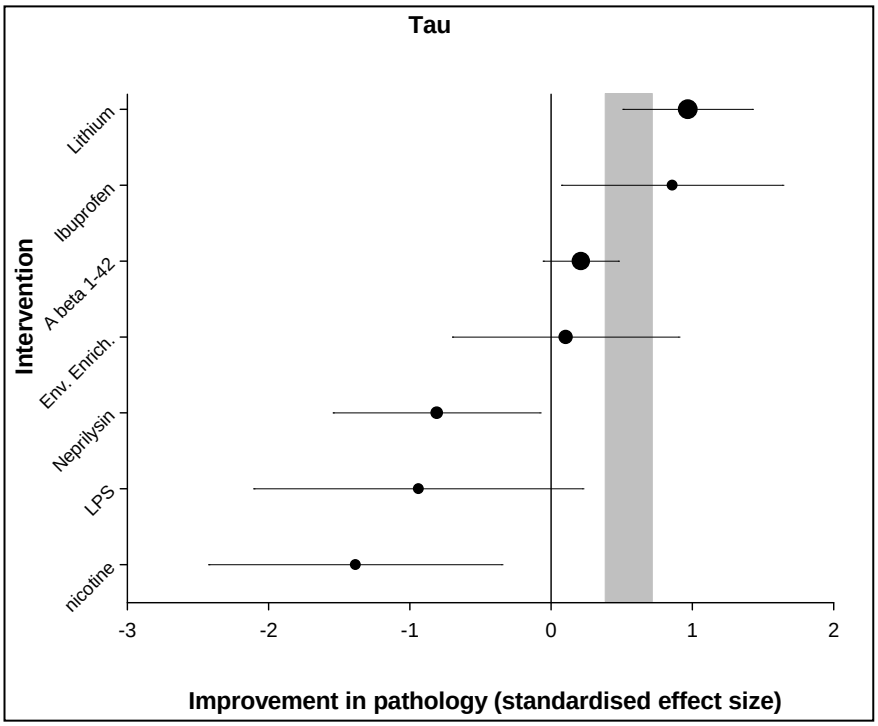


Figure 6.4: Interventions which were examined in five or more publications are stratified according to tau estimates of effect size. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Grey bar represents 95% CI across all interventions.

6.1.5 Cellular infiltrates

Within the 16 most commonly reported outcomes, 10 interventions reported changes in cellular infiltrates. Cerebrolysin was associated with the greatest reduction of cellular infiltrates with an estimated effect size of 1.05 SD (0.17 to 1.93) although data were limited (2 experiments). Conversely, one experiment which assessed the impact of antibody 10d5 suggested an increase in cellular infiltrates of -1.96 (-6.08 to 2.17).

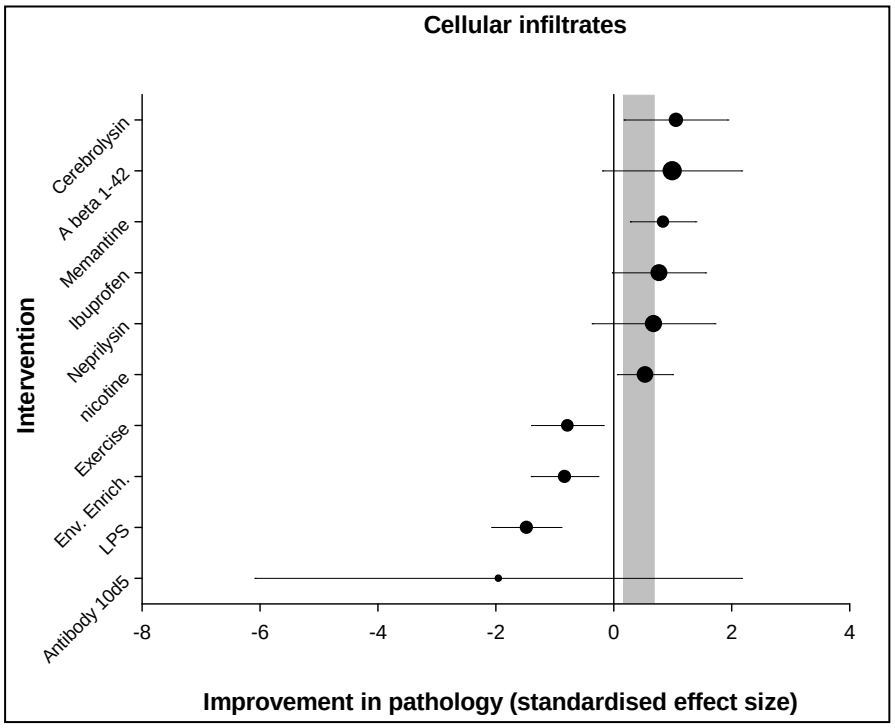


Figure 6.5: Interventions which were examined in five or more publications are stratified according to cellular infiltrates estimates of effect size. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Grey bar represents 95% CI across all interventions

6.1.6 Neurodegeneration

Twelve of the 16 most frequently reported interventions assessed changes in neurodegeneration. Antibody 3d6 was associated with the greatest improvement in neurodegeneration, with an effect size of 1.80 SD (1.08 to 2.52). Smaller effect sizes were associated with Memantime where the overall estimate across 4 experiments crossed the line of no effect 0.12 SD (-0.44 to 0.68). Interestingly, while 55 experiments investigated the use of amyloid beta 42 overall, only 1 experiment examined neurodegeneration outcomes where there was an overall improvement of 1.22 SD (0.39 to 2.04).

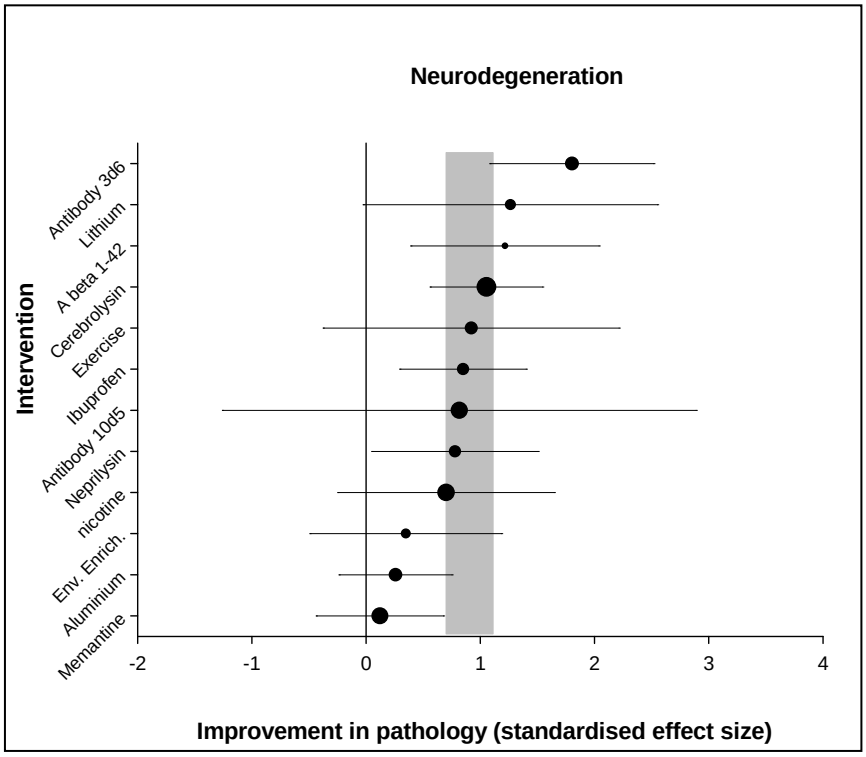


Figure 6.6: Interventions which were examined in five or more publications are stratified according to neurodegeneration estimates of effect size. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Grey bar represents 95% CI across all interventions

Intervention	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	TAU SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neuro-degeneration SMD Effect size (95 % CI) and N
A beta 1-42 55 experiments	1.49 (1.18 to 1.80) **42**	1.48 (0.81 to 2.15) **20**	1.07 (0.71 to 1.42) **28**	0.21 (-0.06 to 0.48) **5**	0.99 (-0.19 to 2.17) **6**	1.22 (0.39 to 2.04) **1**
LY-411575 22 experiments	1.68 (1.15 to 2.21) **1**	2.15 (1.43 to 2.87) **22**	1.67 (0.78 to 2.56) **9**	No data	No data	No data
Lithium 15 experiments	3.83 (-2.19 to 9.86) **2**	1.48 (-1.5 to 4.45) **2**	5.40 (2.84 to 7.95) **7**	0.97 (0.51 to 1.42) **9**	No data	1.26 (-0.03 to 2.55) **1**
Envir. Enrich 12 experiments	0.4 (-0.18 to 0.97) **9**	-0.45 (-1.72 to 0.82) **5**	-0.39 (-1.66 to 0.88) **5**	0.1 (-0.7 to 0.9) **1**	-0.84 (-1.4 to -0.27) **1**	0.35 (-0.49 to 1.19) **1**
Antibody 10d5 10 experiments	1.74 (0.8 to 2.67) **8**	0.16 (-0.51 to 0.83) **1**	0.14 (-0.53 to 0.81) **1**	No data	-1.96 (-6.08 to 2.17) **1**	0.82 (-1.26 to 2.89) **2**
LPS 10 experiments	0.89 (0.16 to 1.63) **9**	-0.48 (-1.19 to 0.23) **1**	-0.32 (-1.02 to 0.38) **1**	-0.94 (-2.1 to 0.22) **1**	-1.48 (-2.07 to -0.9) **2**	No data
Ibuprofen 9 experiments	1.09 (0.70 to 1.49) **5**	0.40 (-0.17 to 0.98) **5**	0.21 (-0.31 to 0.74) **6**	0.86 (0.07 to 1.64) **1**	0.77 (-0.02 to 1.56) **4**	0.85 (0.29 to 1.4) **1**
Cerebrolysin 8 experiments	1.24 (0.78 to 1.7) **8**	0.23 (-0.91 to 1.37) **1**	0.88 (-0.33 to 2.1) **1**	No data	1.05 (0.17 to 1.93) **2**	1.05 (0.56 to 1.55) **5**
Exercise 8 experiments	0.54 (-0.39 to 1.46) **4**	0.71 (-0.1 to 1.52) **2**	1.08 (-0.24 to 2.39) **4**	No data	-0.79 (-1.4 to -0.18) **1**	0.92 (-0.37 to 2.22) **2**
Flurbiprofen 8 experiments	0.89 (-0.74 to 2.52) **2**	0.21 (0 to 0.42) **8**	0.13 (-0.09 to 0.35) **8**	No data	No data	No data
Nicotine 7 experiments	1.28 (0.1 to 2.46) **4**	1.14 (0.52 to 1.76) **7**	1.39 (0.46 to 2.33) **7**	-1.39 (-2.42 to -0.35) **1**	0.53 (0.06 to 1) **1**	0.7 (-0.25 to 1.65) **3**
Neprilysin 6 experiments	0.99 (0.37 to 1.6) **5**	0.91 (0.54 to 1.28) **2**	1.3 (-0.21 to 2.82) **2**	-0.81 (-1.54 to -0.08) **1**	0.67 (-0.37 to 1.71) **2**	0.78 (0.05 to 1.51) **1**
A beta 1-15 5 experiments	1.48 (0.76 to 2.19) **5**	0.02 (-0.4 to 0.43) **4**	0.15 (-0.25 to 0.55) **5**	No data	No data	No data
Memantine 5 experiments	1.54 (0.94 to 2.15) **4**	0.86 (-0.72 to 2.43) **1**	0.33 (-1.67 to 2.33) **1**	No data	0.83 (0.28 to 1.39) **1**	0.12 (-0.44 to 0.68) **4**
Aluminium 4 experiments	-1.27 (-2.07 to -0.47) **1**	-0.21 (-1.77 to 1.35) **3**	0.05 (-1.42 to 1.52) **3**	No data	No data	0.26 (-0.24 to 0.75) **2**
Antibody 3d6 1 experiment	2.24 (1.14 to 3.33) **1**	No data	1.72 (0.72 to 2.72) **1**	No data	No data	1.8 (1.08 to 2.52) **1**

Key: Significant improvement | Non. sig. improvement | Non. sig. worsening | Significant worsening

Table 6.1 (previous page): The sixteen most commonly tested interventions were assessed for their ability to reduce the most commonly reported pathological features of Alzheimer's disease: plaque burden, amyloid beta 40, amyloid beta 42, tau, cellular infiltrates and neurodegeneration. Effect sizes are given in standardised effect size, brackets give 95% confidence limits and number of experiments. Environmental enrichment (Envir. Enrich).

Neurobehavioural outcomes

For neurobehavioural outcomes, I first derived estimates for the sixteen most commonly tested interventions collectively across the most commonly used paradigms. To account for potential differences in paradigms used I then summarise intervention data for the acquisition phase of the Morris water maze, the probe phase of the Morris water maze and other behavioural paradigms separately. Summaries follow this order to reflect the lesser need to demonstrate neurobehavioural improvements by individual outcomes (the need is greater for pathological outcomes where targeting specific molecular structures may be important for achieving clinical efficacy).

6.1.7 All neurobehavioural outcomes

For neurobehavioural data overall, 13 out of the 16 most commonly assessed interventions reported behavioural outcomes (Table 6.2 for overview). Within such studies neprilysin was associated with larger effect sizes of 1.36 SD (0.52 to 2.20, Figure 6.6) however such estimates were based only two experiments. Interestingly, Memantime (which is clinical use) was associated with only a modest benefit in behaviour of 0.28 SD (-0.03 to 0.58). The most commonly assessed neurobehavioural intervention overall was amyloid beta 1-42 which featured in 23 experiments and data suggested an improvement of 0.72 SD (0.44 to 1.00).

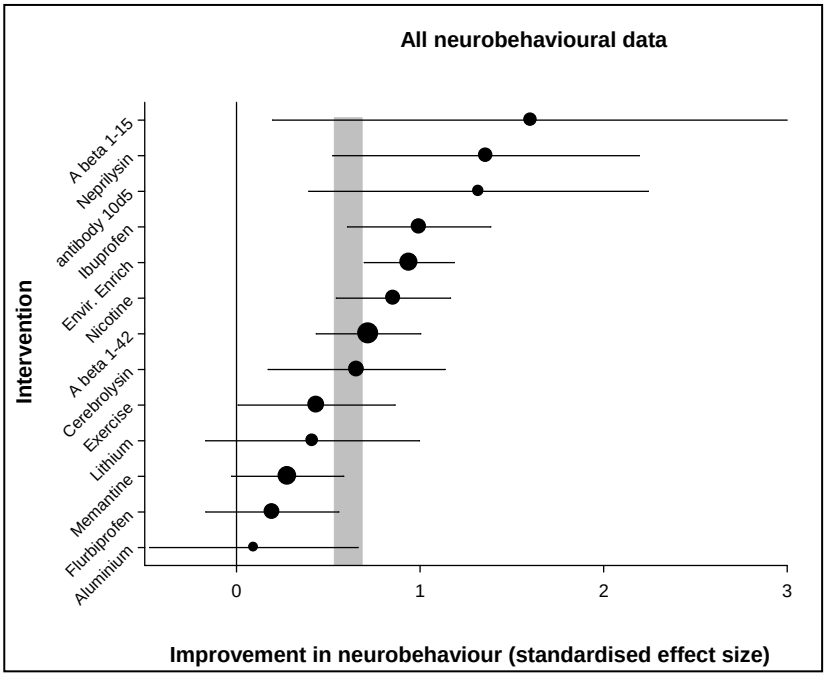


Figure 6.7: Interventions with outcomes reported in five or more publications were stratified according to overall neurobehavioural estimates of effect size. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Environmental enrichment (Env. Enrich)

6.1.8 Acquisition phase of the MWM

Within the most commonly reported interventions twelve reported outcomes within the acquisition phase of the MWM (Figure 6.8). Lithium was associated with the greatest estimates of effect size of 1.67 SD (0.68 to 2.65, [1 experiment]) whereas the use of aluminium was associated with effect sizes which crossed the line of no effect 0.26 SD (-0.72 to 1.25, [1 experiment]). Memantine, which crossed the line of no effect for neurobehaviour overall, was associated with significant improvements of 0.41 SD (0.04 to 0.78) from 5 experiments.

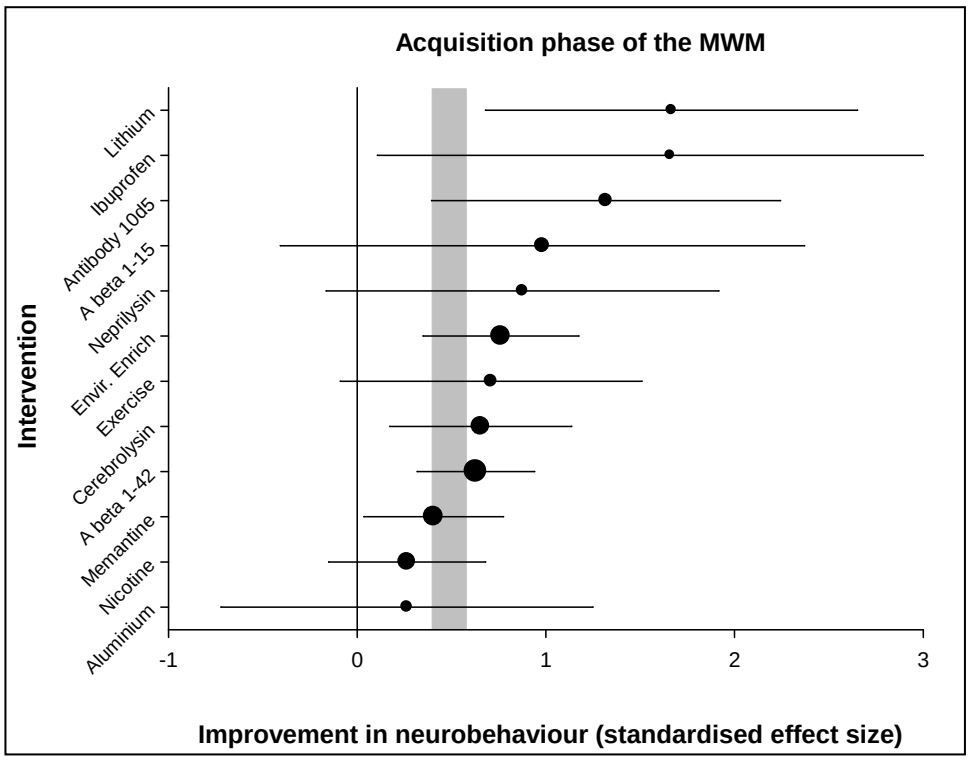


Figure 6.8: Interventions with outcomes reported in five or more publications were stratified according to overall performance in the acquisition phase of the Morris water maze (MWM). Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals. Environmental enrichment (Env. Enrich)

6.1.9 Probe phase of the MWM

Eleven out of the sixteen most commonly reported data from the probe phase of the Morris water maze. Amyloid beta 1-15 was associated with the greatest estimates of effect size (1.61 [-0.19 to 3.42], 3 experiments)whereas lithium was associated with a modest worsening of outcome (-0.04 (-0.85 to 0.76 [1 experiment]). The most commonly reported outcome was amyloid beta 1-42 which featured in 13 experiments suggesting an effect size of 0.88 SD (0.53 to 1.24).

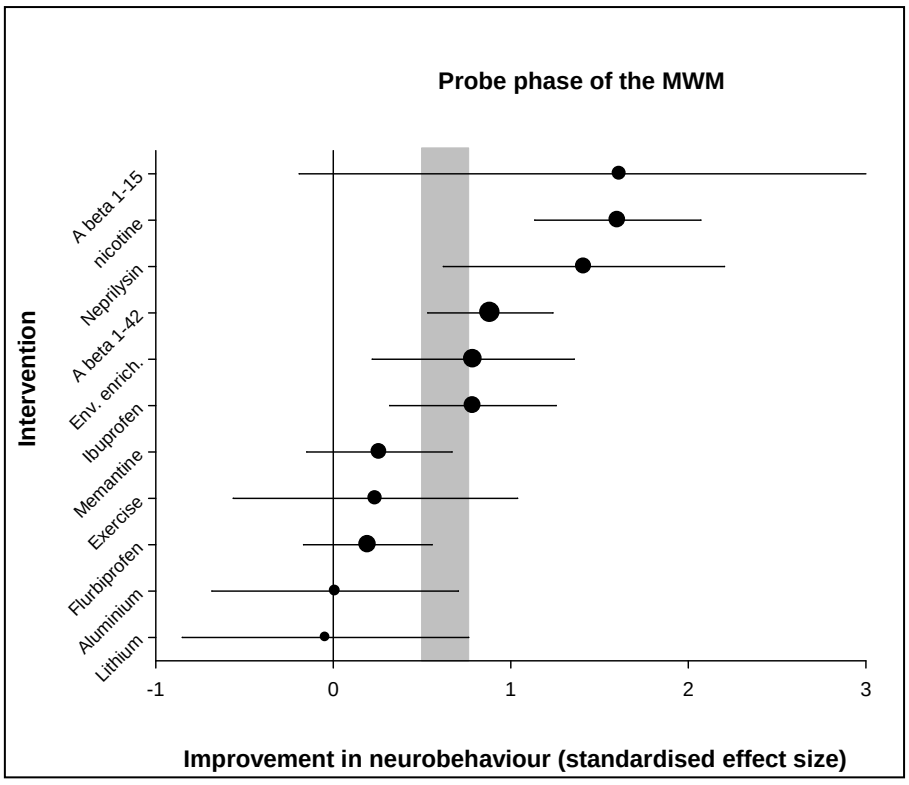


Figure 6.9 : Interventions with outcomes reported in five or more publications were stratified according to overall performance in the probe phase of the Morris water maze (MWM). Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals

6.1.10 Other neurobehavioural data

Seven of the 16 most commonly reported interventions were tested in the RAWM or NORT, Fear conditioning or T/Y maze. While data were more limited overall, I derived estimates of efficacy and found lower estimates of effect size with lithium of 0.03 SD (-0.85 to 0.90), [1 experiment]. Amyloid beta 1-15 was associated with greater effect sizes of 2.46 SD (0.10 to 4.82). Similar to the acquisition and probe phase of the MWM, the greatest number of experiments were performed on amyloid beta 1-42 (7 experiments) which was associated with an improvement of 0.62 but 95% confidence limits crossed the line of no effect (-0.14 to 1.38).

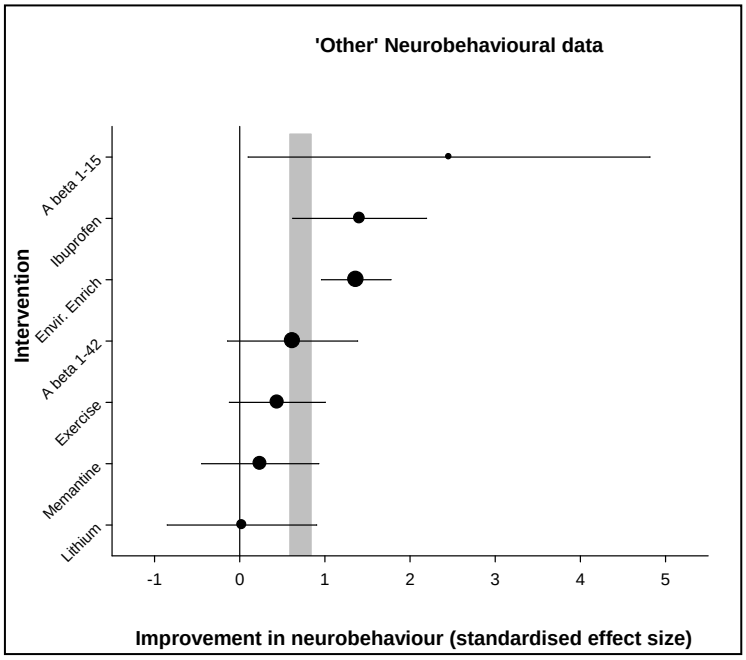


Figure 6.10: Interventions with outcomes reported in five or more publications were stratified according to overall performance across the novel object recognition task, fear conditioning, radial am water maze and T/Y maze. Error bars represent 95% Confidence limits of summary estimate and symbol size represents the log of the number of animals.

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other NBS SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
A beta 1-42	0.63 (0.32 to 0.94) **15**	0.88 (0.53 to 1.24) **13**	0.62 (-0.14 to 1.38) **7**	0.72 (0.44 to 1) **23**
Memantine	0.41 (0.04 to 0.78) **5**	0.26 (-0.15 to 0.67) **4**	0.24 (-0.45 to 0.93) **4**	0.28 (-0.03 to 0.58) **9**
Environmental Enrichment	0.76 (0.35 to 1.17) **6**	0.79 (0.22 to 1.36) **7**	1.37 (0.96 to 1.78) **7**	0.94 (0.7 to 1.19) **9**
Exercise	0.71 (-0.09 to 1.51) **2**	0.24 (-0.56 to 1.04) **4**	0.44 (-0.12 to 1) **4**	0.44 (0.01 to 0.86) **8**
A beta 1-15	0.98 (-0.41 to 2.37) **3**	1.61 (-0.19 to 3.42) **3**	2.46 (0.1 to 4.82) **1**	1.60 (0.2 to 3.01) **4**
Cerebrolysin	0.66 (0.17 to 1.14) **3**	No data	No data	0.66 (0.17 to 1.14) **3**
Nicotine	0.26 (-0.15 to 0.68) **3**	1.60 (1.13 to 2.07) **3**	No data	0.86 (0.54 to 1.17) **3**
Ibuprofen	1.66 (0.11 to 3.21) **1**	0.79 (0.32 to 1.26) **3**	1.41 (0.62 to 2.19) **1**	1 (0.61 to 1.39) **3**
Flurbiprofen	No data	0.19 (-0.17 to 0.56) **2**	No data	0.19 (-0.17 to 0.56) **2**
Lithium	1.67 (0.68 to 2.65) **1**	-0.04 (-0.85 to 0.76) **1**	0.03 (-0.85 to 0.9) **1**	0.41 (-0.17 to 1) **2**
Neprilysin	0.88 (-0.16 to 1.92) **1**	1.41 (0.62 to 2.2) **2**	No data	1.36 (0.52 to 2.19) **2**
Aluminium	0.26 (-0.72 to 1.25) **1**	0.01 (-0.68 to 0.71) **1**	No data	0.09 (-0.47 to 0.66) **1**
antibody 10d5	1.32 (0.39 to 2.24) **1**	No data	No data	1.32 (0.39 to 2.24) **1**
Antibody 3d6	No data	No data	No data	No data
LPS	No data	No data	No data	No data
LY-411575	No data	No data	No data	No data

Key: Significant improvement | Non. sig. improvement | Non. sig. worsening | Significant worsening

Table 6.2 The sixteen most commonly tested interventions summarised for their ability to improve overall neurobehaviour and more specifically, the acquisition and probe phase of the Morris water maze (MWM) and other neurobehavioural paradigms. Effect sizes are given in standardised effect size, brackets give 95%

6.2 Analyses regarding individual interventions or intervention groups

One advantage of systematic review techniques is the ability to empirically quantify the impact of intervention administration study design characteristics such as; the dose, number of administrations or route of administration used. However, within those interventions which report outcomes in 5 or more publications there were generally insufficient data (or detail) to perform such analyses (Table 6.2). Where I was able to analyse data was where amyloid fragments had been used as an active immunisation strategy.

For active immunisation using amyloid beta fragments there were a number of different variations of amyloid experiments used (e.g. gene or peptide, specific fragment of amyloid). From our summaries in Chapter 3 I concluded that the method of modification of active immunisation fragments was too varied to permit reliable analysis to assess whether the different modifications made to amyloid fragments are associated with differences in observed efficacy. Sufficient data were present I investigated the active immunisation dataset further to address: (i) whether I observe differences in efficacy between gene and peptide immunisation and (ii) whether N terminal fragments perform better than amyloid beta 1-42 .

6.2.1 Dose analyses

Intervention	Dose	Unit	Total
A beta 1-42	1	ul/350 uM	1
	35	ul/350 uM	1
	100	µg	1
		mg	2
	200	µg	1
	Unknown		49
A beta 1-42 Count			55
LY-411575	0.1	mg/kg/day	2
	0.3	mg/kg/day	2
	1	mg/kg/day	3
	3	mg/kg/day	3
	10	mg/kg/day	11
	25	mg/kg/day	1
LY-411575 Count			**22**
Lithium	1.98	g/kg	1
	2	LICL/kg	3
	2.4	mg/kg/day	1
	10	microlitres per gram	1
	20	mg/kg/day	1
	60	mg/kg/day	1
	200	mg/kg/day	1
	300	mg/kg/day	3
	600	mg/kg/day	1
	Unknown		2
Lithium Count			**15**
Environmental Enrichment	Unknown		12
Environmental Enrichment Count			12
Antibody 10d5	10	mg/kg/week	2
	Unknown		8
Antibody 10d5 Count			10
LPS	0.5	mg/kg	1
	4	ug/ul	2
	10	ug	3
	25	mg/kg	2
	Unknown		2
LPS Count			**10**
Ibuprofen	40	mg/kg/day	1
	50	mg/kg/day	2
	56	mg/kg/day	1
	62.5	mg/kg/day	2
	375	ppm	3

Intervention	Dose	Unit	Total
Ibuprofen Count			**9**
Cerebrolysin	4	mg/kg	1
	5	mg/kg	2
		ml/kg	5
Cerebrolysin Count			8
Exercise	2520	mins	1
	4850	mins	1
	Unknown		6
Exercise Count			8
Flurbiprofen	10	mg/kg/day	4
	25	mg/kg/day	2
	50	mg/kg/day	1
	100	mg/kg/day	1
Flurbiprofen Count			8
Nicotine	0.42	mg/kg	2
	30	mg/kg	1
	195	ug/day	1
	200	ug/mL	2
	490	ug/mL	1
Nicotine Count			**7**
Neprilysin	0.6	µl	2
	2	µl	1
	3	µl	1
	4	µl	1
	15000000	TU	1
Neprilysin Count			**6**
A beta 1-15	Unknown		5
A beta 1-15 Count			**5**
Memantine	5	mg/kg/day	1
	10	mg/kg/day	3
	20	mg/kg/day	1
Memantine Count			**5**
Aluminium	0.09	mg/g	2
	2	mg/kg/diet	1
	17	mg/kg/day	1
Aluminium Count			**4**
Antibody 3d6	10	mg/kg/week	1
Antibody 3d6 Count			**1**

Table 6.2: From the most commonly tested interventions, there were too few experiments to power analyses into examining the impact of dose across any outcome. Data described represents intervention dose and individual experiments conducted.

6.2.2 Active immunisation analyses

I stratified individual pathological outcomes according to whether active immunisation experiments were performed using amyloid peptides or genes. Our analyses suggested that active immunisation strategies successfully reduced the extent of plaque burden, amyloid beta 40 and 42, neurodegeneration and neurobehaviour in transgenic animals. I observed significantly smaller estimates of effect size using peptides for plaque burden, amyloid beta 40, amyloid beta 42 and neurodegeneration. For cellular infiltrates both estimates crossed the line of no effect (Figure 6.11 and Table 6.3).

	Peptide SMD Effect size (95 % CI) and N	Gene SMD Effect size (95 % CI) and N	Global SMD Effect size (95 % CI) and N	Chi- squared
Plaque area	0.98 (0.75 to 1.2) 54	1.91 (1.43 to 2.39) 25	1.24 (1.02 to 1.46) 79	160.3 Sig.
Amyloid beta 40	0.55 (0.51 to 1.14) 30	2.09 (1.02 to 2.42) 12	0.83 (0.65 to 1.12) 42	86.6 Sig.
Amyloid beta 42	0.69 (0.47 to 0.92) 42	1.72 (1.02 to 2.42) 16	0.88 (0.65 to 1.12) 58	93.8 Sig.
Tau	0.26 (-0.07 to 0.59) 3	0.29 (-0.2 to 0.79) 3	0.28 (0.05 to 0.51) 6	0.44 Non sig.
Cellular infiltrates	0.5 (-0.28 to 1.28) 12	0.05 (-1.32 to 1.42) 4	0.39 (-0.26 to 1.05) 16	75.6 Sig.
Neurodegeneration	0.84 (0.32 to 1.37) 6	No data	0.84 (0.32 to 1.37) 6	
Neurobehaviour	0.97 (0.77 to 1.17) 16	0.75 (0.26 to 1.25) 23	0.81 (0.51 to 1.12) 36	2.97 Non sig.

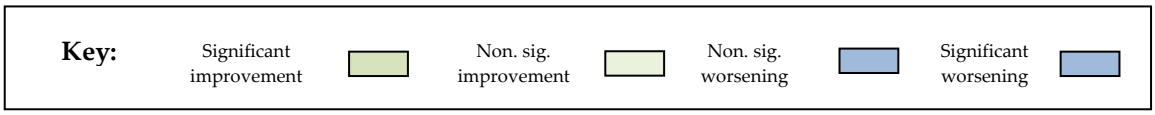


Table 6.3: I stratified active immunisation outcomes using amyloid fragments according to whether they used a gene or peptide Estimates of efficacy are given in terms of standardises effect size, 95% confidence limits and number of experiments.

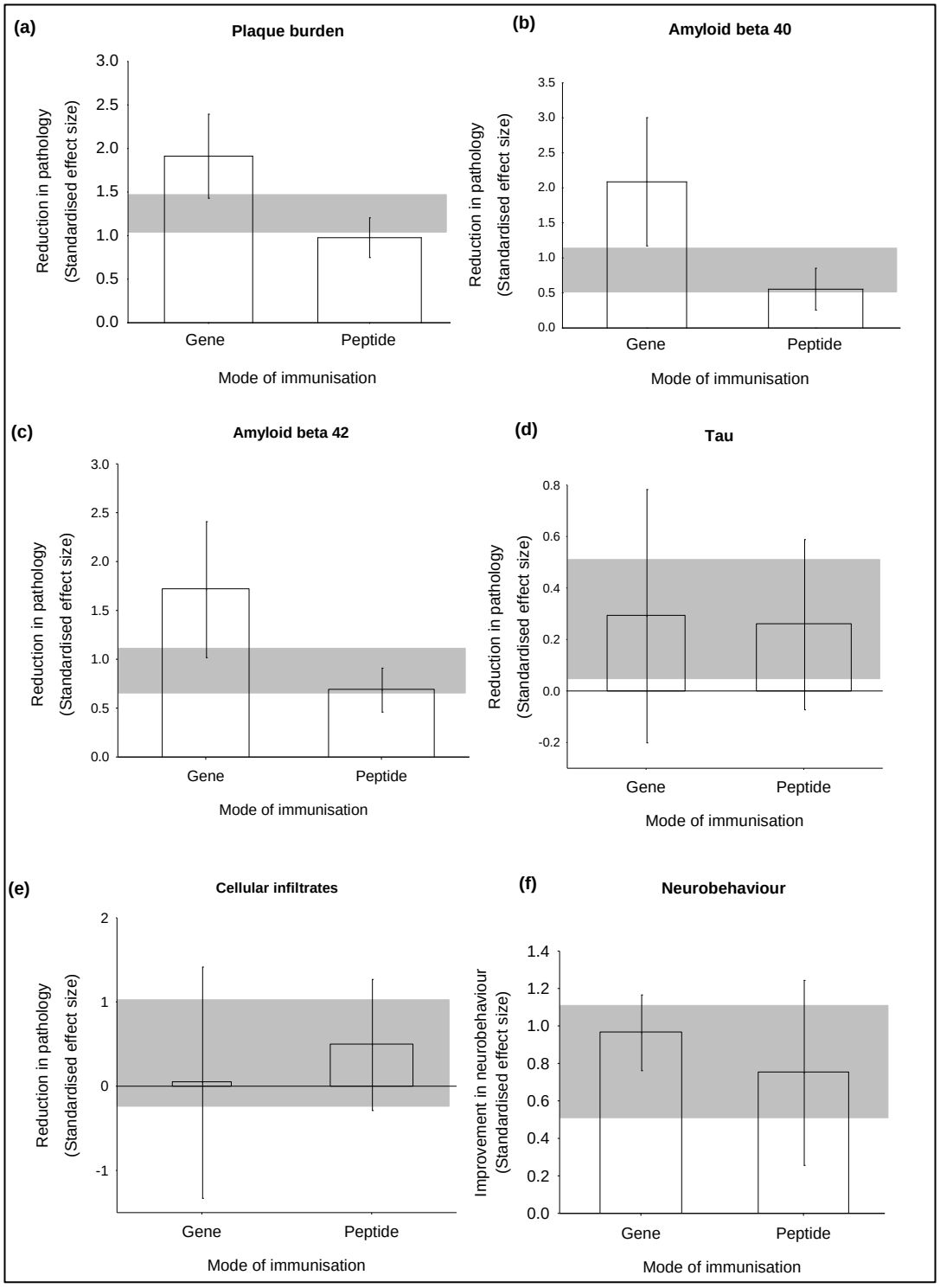

(a)
Plaque burden
Reduction in pathology (Standardised effect size)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Gene
Peptide
Mode of immunisation
(b)
Amyloid beta 40
Reduction in pathology (Standardised effect size)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Gene
Peptide
Mode of immunisation
(c)
Amyloid beta 42
Reduction in pathology (Standardised effect size)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Gene
Peptide
Mode of immunisation
(d)
Tau
Reduction in pathology (Standardised effect size)
0.8
0.6
0.4
0.2
0.0
-0.2
Gene
Peptide
Mode of immunisation
(e)
Cellular infiltrates
Reduction in pathology (Standardised effect size)
2
1
0
-1
Gene
Peptide
Mode of immunisation
(f)
Neurobehaviour
Improvement in neurobehaviour (Standardised effect size)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Gene
Peptide
Mode of immunisation

Figure 6.11 (previous page): I inspected estimates of efficacy for active immunisation fragments according to whether amyloid was administered as gene or petide. Figure shows stratified estimates across plaque burden, amyloid beta 40, amyloid beta 42, tau and cellular infiltrates. Error bars represent 95% CI, grey bar denotes 95 CI of global estimate. Chi squared values given in Table 6.3.

As there a number of different fragments of amyloid used in active immunisation I sought to understand whether the specific fragment used would impact on observed efficacy for plaque burden. Thus, I dichotomised data into experiments which used full length amyloid beta 1-42 and N terminal fragments however I did not find observe significant differences between these two groups (Figure 6.12, χ^2 =2.82).

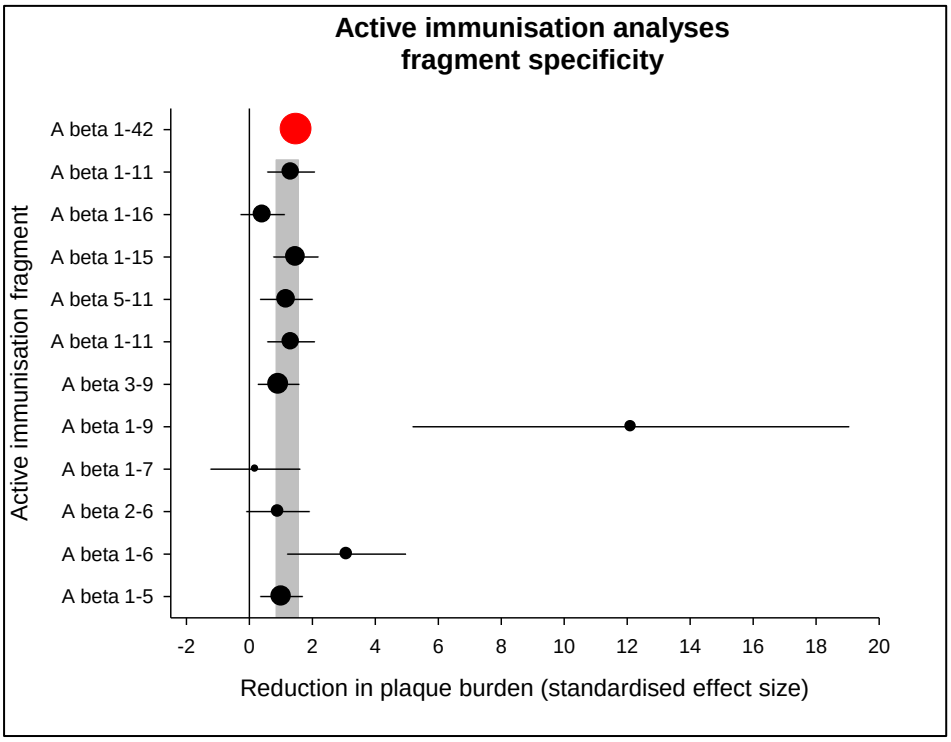


Figure 6.12 (previous page): I examined estimates of efficacy for amyloid beta fragments on plaque burden but did not find significant differences between short N terminal fragments (black) and amyloid beta 42 (red). Error bars represent 95% confidence limits (CI), grey bar denotes 95% CI of fragments near the N-terminus, symbol size represents the log of the number of animals.

6.3 Summary estimates for interventions

For each intervention assessed in transgenic mouse models of AD I provide summary estimates using standardised mean difference across pathology and neurobehaviour. Estimates are frequently calculated using few data, and therefore results should be interpreted with caution, particularly where estimates are extreme.

Two hundred and seventy three interventions were assessed for their ability to improve pathological outcomes (Table 6.3). While estimates are given for each individual pathological outcome, the order of interventions is based on the overall reduction of across all pathologies. 107 interventions were assessed for their ability for their ability to improve neurobehavioural outcomes (Table 6.4). For neurobehavioural outcomes, estimates of efficacy are ordered in terms of overall improvements in neurobehaviour, and I provide estimates of efficacy overall and summarise individual groups of behavioural data. Whilst this approach is informative for assessing potential strengths and weaknesses across the different apparatus used, it is unlikely that intervention development is paradigm specific and I would regard behaviour overall as the most useful indicator.

6.3.1 Heat map for pathological outcomes

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Antibody anti-beta 3-6	7.6 (-0.4 to 15.6) 1	No data	No data	No data	No data	No data
Antibody 4G8	13.3 (0.36 to 26.23) 1	No data	No data	5.66 (-0.04 to 11.35) 1	No data	No data
Antibody 1E11(anti A beta 1-10)	6.81 (-0.43 to 14.05) 1	No data	No data	No data	No data	No data
BMS-433796	No data	6.35 (3.38 to 9.32) 1	No data	No data	No data	No data
NGF	6.02 (0.23 to 11.8) 2	No data	No data	No data	No data	No data
Antibody anti-beta 1-28	5.89 (-0.48 to 12.26) 1	No data	No data	No data	No data	No data
Umbilical Cord Blood Cells	6.2 5.15 to 7.26) 1	No data	No data	No data	5.44 (4.35 to 6.53) 1	No data
Garlic extract	12.56 (1.87 to 23.25) 1	6.46 (2.64 to 10.28) 4	9.65 (2.87 to 16.43) 4	2.56 (-0.21 to 5.34) 1	No data	No data
Antibody 2H4 (anti A beta 1-10)	5.75 (-0.49 to 11.99) 1	No data	No data	No data	No data	No data
ST1571	No data	No data	No data	4.7 (1.16 to 8.24) 1	No data	5 (-0.09 to 10.09) 1
Antibody IgG2b (anti A-beta 1-40)	4.45 (-0.6 to 9.5) 1	No data	No data	No data	No data	No data
Furin		5.89 (3.37 to 8.42) 2	3.8 (-1.04 to 8.64) 2	No data	No data	No data
Antibody (fusion)	4.27 (1.1 to 7.45) 1	No data	No data	No data	No data	No data
KEGV	4.19 (-1.11 to 9.48) 2	No data	No data	No data	No data	No data
MRK-560	0.67 (0.06 to 1.28) 1	6.12 (-1.87 to 14.11) 4	1.08 (0.45 to 1.71) 3	No data	1.55 (-0.64 to 3.74) 1	No data
H89	No data	No data	3.92 (2.3 to 5.53) 1	No data	No data	No data
Antibody A11	5.12 (2.3 to 7.93) 2	3.42 (1.34 to 5.51) 1	3.16 (1.18 to 5.14) 1	5.24 (1.38 to 9.1) 1	No data	No data
Antisense Beta-site ODN	No data	5.81 (0.16 to 11.45) 1	3.08 (-0.35 to 6.5) 1	No data	No data	No data
Antibody anti-beta-11	3.48 (-4.12 to 11.09) 2	No data	No data	No data	No data	No data
Epigallocatechin-3-gallate	3.91 (2.35 to 5.48) 1	3.35 (2.32 to 4.38) 1	3 (2.02 to 3.97) 1	No data	No data	No data
Merk-3	No data	4.26 (0.65 to 7.87) 4	3.03 (1.8 to 4.26) 4	No data	No data	No data
Antibody 1560	4.79 (1.32 to 8.26) 6	No data	No data	3.5 (0.78 to 6.22) 6	No data	No data
DADS	5.13 (0.48 to 9.77) 1	14.52 (5.81 to 23.24) 1	7.76 (2.98 to 12.53) 1	1 (-0.94 to 2.95) 1	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Alpha- tocopherol	No data	No data	No data	2.79 (-0.1 to 5.69) 4	No data	No data
BMS-299897 (also known as SIB-3520)	No data	2.62 (1.13 to 4.11) 11	No data	No data	No data	No data
Antibody scFv40.1	1.27 (-0.39 to 2.94) 1	5.57 (1.93 to 9.21) 1	5.4 (1.85 to 8.95) 1	No data	No data	No data
Pravastatin	1.08 (-0.43 to 2.6) 4	2.46 (0.61 to 4.31) 4	4.89 (2.02 to 7.76) 4	No data	No data	No data
Grape Polyphenolics	No data	2.66 (0.71 to 4.6) 1	2.17 (0.43 to 3.91) 1	No data	No data	No data
BMS-289948 (also known as SIB-3399)	No data	2.35 (0.75 to 3.95) 6	No data	No data	No data	No data
TTR antibody	No data	No data	No data	No data	No data	2.26 (0.69 to 3.82) 1
Antibody 16G1	No data	No data	2.22 (0.12 to 4.31) 1	No data	No data	No data
Lithium	3.83 (-2.19 to 9.86) 2	1.48 (-1.5 to 4.45) 2	5.4 (2.84 to 7.95) 7	0.97 (0.51 to 1.42) 9	No data	1.26 (-0.03 to 2.55) 1
CA074Me	2.57 (-1.75 to 6.9) 2	1.85 (-1.16 to 4.85) 2	1.71 (-1.27 to 4.68) 2	No data	No data	No data
Y-27632	No data	No data	2.12 (0.98 to 3.26) 1	No data	No data	No data
A beta 1-6	3.09 (1.2 to 4.97) 1	1.06 (-0.19 to 2.3) 1	4.48 (2.02 to 6.94) 1	No data	No data	No data
Antibody anti-beta-13	No data	1.86 (0.83 to 2.88) 3	2.14 (1.25 to 3.03) 3	No data	No data	No data
CNI-1493	2.01 (1.07 to 2.95) 1	No data	No data	No data	No data	No data
Antibody p-F(ab')2	No data	1.81 (0.81 to 2.81) 3	2.14 (1.29 to 2.98) 3	No data	No data	No data
Antibody Amy-33	1.56 (0.1 to 3.03) 4	20.43 (9.74 to 31.12) 1	23.43 (10.91 to 35.95) 1	No data	5.69 (3.76 to 7.63) 1	No data
Atorvastatin	1.52 (0.34 to 2.69) 1	3.01 (1.44 to 4.57) 1	1.85 (0.6 to 3.1) 1	No data	No data	No data
SAC	8.11 (1.08 to 15.14) 1	15.97 (6.08 to 25.85) 1	1.05 (-0.7 to 2.81) 1	2.11 (-0.38 to 4.6) 1	No data	No data
N-acetyl cystine	No data	3.91 (1.15 to 6.68) 1	1.23 (-0.42 to 2.88) 1	No data	No data	No data
Antibody 3d6	2.24 (1.14 to 3.33) 1	No data	1.72 (0.72 to 2.72) 1	No data	No data	1.8 (1.08 to 2.52) 1
Arundic Acid	1.62 (1.36 to 1.87) 1	1.31 (0.73 to 1.88) 1	1.35 (0.77 to 1.93) 1	No data	2.89 (2.52 to 3.27) 1	No data
memoquin	1.51 (0.28 to 2.75) 2	No data	No data	2.07 (0.1 to 4.05) 3	No data	No data
DAPT	No data	1.6 (0.43 to 2.76) 1	2.08 (0.8 to 3.36) 1	No data	No data	No data
Ginsenoside Rg3	No data	1.66 (0.39 to 2.94) 1	1.98 (0.63 to 3.34) 1	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
LY-411575	1.68 (1.15 to 2.21) 1	2.15 (1.43 to 2.87) 22	1.67 (0.78 to 2.56) 9	No data	No data	No data
E64d	2.69 (-1.73 to 7.11) 2	1.53 (-0.82 to 3.88) 2	1.28 (-1.58 to 4.15) 2	No data	No data	No data
Amyloid beta-12-28P	2.13 (1.6 to 2.67) 3	0.87 (-0.49 to 2.23) 3	1.66 (-0.78 to 4.09) 2	No data	No data	No data
Antibody scFv	1.71 (0.3 to 3.12) 1	No data	No data	No data	No data	No data
ERC lesion	3.17 (1.84 to 4.5) 1	1.46 (0.5 to 2.42) 1	1.23 (0.3 to 2.16) 1	No data	No data	No data
Leuprolide	1.7 (0.33 to 3.06) 1	No data	No data	No data	No data	No data
Valproic acid	1.38 (1.13 to 1.63) 6	No data	7.26 (4.95 to 9.56) 1	No data	No data	No data
BRI-Abeta1-40	4.02 (1.99 to 6.05) 1	2.76 (1.14 to 4.39) 1	0.38 (-0.78 to 1.53) 1	No data	No data	No data
PAZ-417	No data	2.03 (1.01 to 3.05) 2	1.35 (0.46 to 2.23) 2	No data	No data	No data
Antibody scFv42.2	1.06 (-0.55 to 2.67) 1	3.03 (-1.4 to 7.46) 2	2.79 (1.12 to 4.47) 2	No data	No data	No data
Caffeine	No data	1.61 (-0.17 to 3.38) 1	1.64 (-0.14 to 3.43) 1	No data	No data	No data
Testosterone	1.58 (0.79 to 2.37) 1	No data	No data	No data	No data	No data
Caloric restriction	0.95 (0.13 to 1.77) 2	1.83 (-0.2 to 3.86) 2	4.4 (-2.52 to 11.32) 2	0.33 (-0.36 to 1.01) 1	1.05 (-0.51 to 2.61) 1	No data
Melatonin	0.17 (-0.61 to 0.94) 2	0.8 (-0.11 to 1.71) 5	0.8 (0.03 to 1.58) 5	No data	No data	4.39 (3.19 to 5.59) 2
Paroxetine	No data	2.28 (1.16 to 3.4) 3	0.31 (-1.26 to 1.88) 1	2.12 (-2.23 to 6.48) 2	No data	No data
Antibody scFv9	0.69 (0.85 to 2.23) 1	1.29 (0.27 to 2.3) 2	2.97 (1.35 to 4.59) 2	No data	No data	No data
CHIP expressing lentivirus	No data	No data	No data	1.48 (0.83 to 2.13) 2	No data	No data
Phenserine	No data	No data	No data	No data	1.46 (-0.67 to 3.59) 1	No data
Nogo-66 recep tor -ec to -Fc	0.96 (-0.1 to 2.02) 1	3.39 (1.72 to 5.07) 1	1.75 (0.54 to 2.96) 1	No data	1.15 (0.06 to 2.24) 1	1.17 (0.07 to 2.26) 1
Galantamine	2.63 (0.44 to 4.82) 2	-0.21 (-1.63 to 1.2) 1	-0.14 (-2.11 to 1.82) 1	No data	No data	1.21 (-0.82 to 3.24) 1
Ginsenoside Re	No data	1.3 (0.26 to 2.34) 1	1.32 (0.28 to 2.36) 1	No data	No data	No data
Nobiletin	1.32 (0.24 to 2.4) 1	1.18 (0.13 to 2.24) 1	1.36 (0.28 to 2.45) 1	No data	No data	No data
Retinoic-acid	2.19 (1.53 to 2.85) 1	No data	No data	No data	0.48 (-0.1 to 1.07) 1	1.43 (0.45 to 2.4) 1
D3	0.88 (-0.26 to 2.01) 1	No data	No data	No data	1.47 (0.59 to 2.34) 1	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Scyllo-cyclohexanehexol	1.69 (0.89 to 2.48) 6	1.62 (0.8 to 2.44) 3	1.22 (0.69 to 1.75) 6	No data	1.71 (-0.22 to 3.64) 3	1.73 (-0.42 to 3.87) 3
Nicotine	1.28 (0.1 to 2.46) 4	1.14 (0.52 to 1.76) 7	1.39 (0.46 to 2.33) 7	-1.39 (-2.42 to -0.35) 1	0.53 (0.06 to 1) 1	0.7 (-0.25 to 1.65) 3
A beta 1-42	1.49 (1.18 to 1.8) 42	1.48 (0.81 to 2.15) 20	1.07 (0.71 to 1.42) 28	0.21 (-0.06 to 0.48) 5	0.99 (-0.19 to 2.17) 6	1.22 (0.39 to 2.04) 1
Valsartan	No data	1.17 (0.45 to 1.89) 2	1.25 (0.52 to 1.97) 2	No data	No data	No data
A beta 1-5	1.02 (0.34 to 1.7) 2	No data	1.45 (0.24 to 2.65) 1	No data	No data	1.38 (0.54 to 2.23) 1
EFRH	No data	1.4 (0.4 to 2.39) 3	1.86 (0.74 to 2.98) 3	No data	0.85 (0.24 to 1.46) 1	1.26 (0.75 to 1.78) 1
Cabernet Sauvignon	No data	1.03 (0.15 to 1.91) 1	1.36 (0.41 to 2.31) 1	No data	No data	No data
Fish oil-based diet	No data	No data	1.22 (-0.22 to 2.66) 1	No data	1.15 (-0.28 to 2.58) 1	No data
A beta 5-11	1.18 (0.34 to 2.01) 1	No data	No data	No data	No data	No data
Lovastatin	0.88 (-0.99 to 2.75) 6	0.54 (-0.72 to 1.81) 6	1.3 (-0.33 to 2.93) 6	No data	No data	No data
Copper	1.57 (0.73 to 2.41) 2	1.27 (-1.9 to 4.44) 2	1.89 (-2.65 to 6.43) 2	No data	No data	No data
Endothelin Converting Enzyme (ECE)	1.15 (0.61 to 1.7) 2	No data	No data	No data	No data	No data
AR-A014418	No data	No data	No data	1.15 (0.19 to 2.11) 1	No data	No data
MDVFMKGLSMAKE	1.13 (-3.29 to 5.55) 2	No data	No data	No data	No data	No data
Antibody Ab3	No data	1.21 (-0.24 to 2.67) 1	1.04 (-0.34 to 2.41) 1	No data	No data	No data
Oxybutynin	No data	No data	1.09 (0.01 to 2.17) 2	No data	No data	No data
Cerebrolysin	1.24 (0.78 to 1.7) 8	0.23 (-0.91 to 1.37) 1	0.88 (-0.33 to 2.1) 1	No data	1.05 (0.17 to 1.93) 2	1.05 (0.56 to 1.55) 5
Bacopa Monniera	No data	1.06 (0.62 to 1.5) 4	1.1 (0.66 to 1.54) 4	No data	No data	No data
Antibody ab9	1.63 (0.18 to 3.08) 2	0.81 (0.25 to 1.36) 4	1.19 (0.52 to 1.86) 4	No data	No data	No data
BM15-766	0.13 (-0.89 to 1.14) 1	1.22 (0.42 to 2.03) 1	1.56 (0.69 to 2.44) 1	No data	No data	No data
Insulin-like Growth fac to r 1	1.53 (0.02 to 3.04) 1	2.06 (0.36 to 3.76) 1	1.43 (-0.05 to 2.91) 1	No data	1.05 (0.43 to 1.66) 1	0.82 (0.23 to 1.42) 1
Lenti-siBACE1-6	0.81 (0.07 to 1.55) 1	No data	1.67 (0.48 to 2.85) 1	No data	No data	No data
Antibody anti-beta 1-15	1.05 (0.21 to 1.9) 1	No data	No data	No data	No data	No data
BRI2	4.5 (2 to 7) 1	0.48 (-2.58 to 3.55) 2	1.46 (-3.29 to 6.2) 2	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
A beta 3-9	0.93 (0.27 to 1.59) 2	No data	1.34 (0.15 to 2.53) 1	No data	No data	1.01 (0.2 to 1.82) 1
Indomethacin	0.63 (0.07 to 1.19) 3	0.62 (-0.05 to 1.29) 3	1.78 (1.2 to 2.37) 3	No data	No data	No data
Antibody 10d5	1.74 (0.8 to 2.67) 8	0.16 (-0.51 to 0.83) 1	0.14 (-0.53 to 0.81) 1	No data	-1.96 (-6.08 to 2.17) 1	0.82 (-1.26 to 2.89) 2
DHA-diet 1	1.93 (-0.15 to 4) 1	0.94 (0.19 to 1.68) 3	0.33 (-0.41 to 1.06) 3	2.61 (0.86 to 4.35) 3	No data	0.66 (-0.47 to 1.79) 1
Interferon-gamma	1.36 (-0.91 to 3.63) 2	No data	No data	No data	-4.59 (-13.31 to 4.13) 1	No data
G-CSF	0.53 (-0.47 to 1.54) 1	No data	No data	No data	No data	1.45 (0.38 to 2.53) 1
mHJ5.1	No data	No data	No data	No data	0.95 (-0.9 to 2.8) 1	
Bryostatin 1	No data	0.96 (-0.18 to 2.1) 2	0.69 (-0.05 to 1.43) 1	No data	No data	No data
A beta 1-11	1.33 (0.57 to 2.08) 2	0.89 (0.19 to 1.59) 4	1.17 (-0.31 to 2.65) 4	0.49 (0.03 to 0.95) 1	2.06 (1.18 to 2.93) 2	No data
iA-beta-5	0.91 (0.38 to 1.43) 3	0.75 (-0.12 to 1.62) 1	0.64 (-0.22 to 1.51) 1	No data	No data	1.68 (0.57 to 2.8) 2
A beta 2-6	0.91 (-0.1 to 1.92) 2	No data	No data	No data	No data	No data
Antibody 12B4	0.9 (-0.21 to 2.02) 2	No data	1.35 (0.4 to 2.29) 1	No data	No data	0.92 (0.39 to 1.44) 2
CHF5074	1.2 (0.75 to 1.65) 1	0.93 (0.42 to 1.44) 1	0.71 (0.25 to 1.17) 1	No data	0.68 (0.09 to 1.27) 1	No data
Enoxaparin (a Heparin)	0.95 (0.07 to 1.82) 1	0.83 (-0.27 to 1.94) 1	No data	No data	No data	No data
KMI-429	No data	1.43 (-0.4 to 3.27) 1	0.56 (-0.9 to 2.02) 1	No data	No data	No data
Resveratrol	No data	No data	No data	No data	0.86 (-1.27 to 3) 1	0.92 (-1.26 to 3.1) 1
epi-cyclohexanehexol	0.94 (0.44 to 1.43) 3	0.89 (-0.31 to 2.09) 3	1.02 (-0.71 to 2.76) 3	No data	1.07 (0.39 to 1.75) 2	No data
Memantine	1.54 (0.94 to 2.15) 4	0.86 (-0.72 to 2.43) 1	0.33 (-1.67 to 2.33) 1	No data	0.83 (0.28 to 1.39) 1	0.12 (-0.44 to 0.68) 4
PBD150	1.3 (0.46 to 2.15) 5	0.6 (-0.2 to 1.4) 7	0.85 (0.32 to 1.39) 7	No data	No data	No data
Glatiramer acetate	2.05 (1.16 to 2.95) 2	No data	No data	No data	-1 (-3.38 to 1.38) 2	2.48 (1.53 to 3.43) 1
Ginsenoside Rg1	No data	0.79 (-0.3 to 1.87) 1	0.86 (-0.24 to 1.96) 1	No data	No data	No data
Antibody 16E6	No data	No data	0.81 (-0.68 to 2.31) 1	No data	No data	No data
Pioglitazone	0.43 (-0.07 to 0.93) 3	0.86 (-0.22 to 1.95) 3	0.47 (-0.34 to 1.28) 3	No data	1.61 (0.33 to 2.89) 3	No data
Antibody 82E1	0.48 (-0.86 to 1.83) 1	No data	1.28 (-0.48 to 3.04) 1	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
m3D6 Fab Fragments	No data	No data	No data	No data	0.77 (-0.99 to 2.54) 1	No data
N-phenethnorcymserine (PEC)		1.13 (0.26 to 2) 1	0.46 (-0.35 to 1.27) 1	No data	No data	No data
Scyllo-inositol	0.73 (0.29 to 1.18) 1	0.74 (0.06 to 1.42) 1	0.87 (0.17 to 1.57) 1	No data	No data	No data
PBT2	1.92 (0.44 to 3.4) 1	0.71 (-0.09 to 1.52) 2	0.51 (-0.1 to 1.11) 2	0.65 (-0.34 to 1.65) 3	No data	0.91 (0.07 to 1.74) 2
a beta 1-16	0.42 (-0.28 to 1.12) 1	0.78 (0.27 to 1.29) 1	0.89 (0.38 to 1.41) 1	No data	No data	No data
Picro toxin	No data	No data	No data	No data	No data	0.74 (0.18 to 1.3) 1
Gelsolin	0.81 (0.04 to 1.58) 3	1.76 (0.86 to 2.67) 1	1.35 (0.51 to 2.19) 1	No data	-0.96 (-2.29 to 0.37) 1	No data
Antibody Ab5	No data	0.55 (-0.76 to 1.85) 1	0.94 (-0.41 to 2.3) 1	No data	No data	No data
Physostigmine	0.72 (-0.21 to 1.64) 1	No data	No data	No data	No data	No data
Neprilysin	0.99 (0.37 to 1.6) 5	0.91 (0.54 to 1.28) 2	1.3 (-0.21 to 2.82) 2	-0.81 (-1.54 to -0.08) 1	0.67 (-0.37 to 1.71) 2	0.78 (0.05 to 1.51) 1
Beta-secretase site ODN	No data	0.66 (-1.39 to 2.7) 1	0.74 (-1.33 to 2.82) 1	No data	No data	No data
NAP	No data	0.79 (-0.09 to 1.66) 1	0.71 (-0.16 to 1.58) 1	0.67 (0.05 to 1.29) 3	No data	No data
Exercise	0.54 (-0.39 to 1.46) 4	0.71 (-0.1 to 1.52) 2	1.08 (-0.24 to 2.39) 4	No data	-0.79 (-1.4 to -0.18) 1	0.92 (-0.37 to 2.22) 2
Antibody 2C1	No data	No data	No data	No data	No data	0.67 (-0.25 to 1.6) 1
Antibody Ab42.2	0.8 (-0.28 to 1.88) 2	0.48 (-0.14 to 1.11) 3	0.83 (-0.22 to 1.87) 3	No data	No data	No data
DHA-diet 2	2.18 (-0.01 to 4.38) 1	0.43 (-0.38 to 1.24) 3	0.22 (-0.6 to 1.03) 3	1.34 (0.38 to 2.31) 3	No data	No data
DP-115	No data	0.12 (-0.67 to 0.91) 2	1.69 (-0.08 to 3.45) 2	No data	No data	No data
Corn oil	No data	No data	0.11 (-1.17 to 1.39) 1		1.35 (-0.13 to 2.82) 1	No data
BMS-562492 (TACE INHIBITOR)	No data	0.49 (-0.61 to 1.6) 1	0.8 (-0.35 to 1.96) 1	No data	No data	No data
DP-109	1.55 (1.05 to 2.05) 1	-0.13 (-0.78 to 0.53) 1	-0.24 (-0.9 to 0.43) 1	No data	No data	No data
Pomegranate juice	0.79 (0.34 to 1.23) 1	0.32 (-0.15 to 0.8) 1	0.75 (0.27 to 1.23) 1	No data	No data	No data
AF267B	1.78 (1 to 2.57) 1	0.07 (-1.02 to 1.17) 1	1.89 (0.98 to 2.8) 1	0.24 (-0.11 to 0.6) 1	No data	No data
Memapsin 2	0.81 (0.35 to 1.27) 2	0.37 (-0.14 to 0.87) 2	0.65 (0.17 to 1.12) 2	No data	No data	No data
Antibody Ab40.1	3 (0.39 to 5.62) 1	0.38 (-0.49 to 1.26) 2	0.55 (-0.76 to 1.86) 2	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Vitamin E	0.47 (-0.33 to 1.26) 2	0.63 (-0.15 to 1.41) 2	0.63 (-0.49 to 1.75) 2	No data	No data	No data
A beta 1-28	0.55 (-0.26 to 1.36) 1	No data	No data	No data	0.57 (-0.25 to 1.4) 1	No data
Ibuprofen	1.09 (0.7 to 1.49) 5	0.4 (-0.17 to 0.98) 5	0.21 (-0.31 to 0.74) 6	0.86 (0.07 to 1.64) 1	0.77 (-0.02 to 1.56) 4	0.85 (0.29 to 1.4) 1
Coenzyme Q10	No data	-0.27 (-1.52 to 0.98) 1	2.13 (0.4 to 3.85) 1	No data	No data	No data
A beta 40/42	3.3 (0.74 to 5.86) 2	0.04 (-0.62 to 0.71) 4	0.72 (0.14 to 1.29) 4	No data	No data	No data
GSK-188909	No data	0.44 (-0.48 to 1.36) 2	0.64 (-0.1 to 1.38) 2	No data	No data	No data
apoE2 (Lenti-vector)	0.62 (-0.09 to 1.33) 5	No data	0.33 (-0.73 to 1.39) 2	No data	No data	No data
Compound XH1	No data	0.53 (-0.51 to 1.58) 1	No data	No data	No data	No data
A beta 1-30	0.81 (-0.17 to 1.8) 4	0.33 (-0.08 to 0.73) 3	0.69 (-0.46 to 1.84) 3	No data	No data	No data
DHA-diet 3	3.16 (0.46 to 5.86) 1	0.22 (-0.53 to 0.97) 3	0.37 (-0.42 to 1.15) 3	1.02 (-0.17 to 2.22) 3	No data	No data
Antibody D-2H6	0.67 (-0.13 to 1.47) 3	No data	No data	No data	0.38 (-0.36 to 1.11) 3	No data
Curcumin	1.59 (0.19 to 3) 2	-0.19 (-1.71 to 1.34) 1	-1.76 (-3.1 to -0.43) 1	No data	-0.16 (-0.88 to 0.55) 1	2.65 (0.89 to 4.41) 1
A beta 1-40	0.82 (0.28 to 1.36) 6	0.33 (-1.21 to 1.87) 1	0.36 (-0.43 to 1.15) 5	No data	-0.34 (-1.06 to 0.39) 1	No data
T cells	No data	-0.03 (-1.1 to 1.04) 3	0.54 (-0.65 to 1.73) 3	No data	0.88 (0.13 to 1.64) 3	No data
4396C (FAB fragments)	0.59 (-0.85 to 2.02) 1	0.27 (-0.6 to 1.15) 3	0.88 (-0.44 to 2.19) 3	No data	No data	No data
A beta 1-15	1.48 (0.76 to 2.19) 5	0.02 (-0.4 to 0.43) 4	0.15 (-0.25 to 0.55) 5	No data	No data	No data
K252a	No data	No data	No data	0.48 (0.24 to 0.71) 1	No data	No data
DHA	0.23 (-0.9 to 1.36) 1	-0.01 (-1.19 to 1.17) 3	1.06 (0.23 to 1.89) 3	No data	No data	0.39 (-0.71 to 1.48) 1
Estrogen	0.25 (-0.67 to 1.18) 3	0.42 (0.08 to 0.75) 8	0.8 (0.04 to 1.57) 7	0.78 (-0.33 to 1.88) 1	No data	No data
Learning	2.28 (0.89 to 3.66) 1	-0.19 (-0.92 to 0.54) 1	0.02 (-0.76 to 0.79) 1	0.74 (0.2 to 1.28) 1	No data	No data
GF120918	No data	0.46 (-0.31 to 1.23) 1	0.42 (-0.35 to 1.19) 1	No data	No data	No data
Antibody 20.1 (monoclonal)	No data	1.87 (-0.63 to 4.36) 2	1.03 (-0.2 to 2.26) 2	0.09 (-0.53 to 0.71) 2	No data	No data
High Fat diet	No data	0.59 (-0.1 to 1.28) 1	0.28 (-0.4 to 0.96) 1	No data	No data	No data
Antibody HT7	0.64 (-1.08 to 2.35) 1	No data	No data	0.24 (-1.38 to 1.85) 1	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Antibody 6E10	0.42 (-0.31 to 1.15) 3	No data	No data	No data	No data	No data
Antibody Ab2	No data	0.39 (-0.9 to 1.68) 1	0.44 (-0.84 to 1.73) 1	No data	No data	No data
Erythromycin	No data	0.16 (-1.32 to 1.65) 1	0.66 (-0.87 to 2.2) 1	No data	No data	No data
Antibody Ib3	0.4 (-1.01 to 1.81) 1	No data	No data	No data	No data	No data
OMOO-3 DR9	No data	0.59 (-0.19 to 0.98) 1	No data	No data	No data	No data
Antibody 3A3	No data	No data	No data	No data	No data	0.39 (-0.51 to 1.3) 1
LPS	0.89 (0.16 to 1.63) 9	-0.48 (-1.19 to 0.23) 1	-0.32 (-1.02 to 0.38) 1	-0.94 (-2.1 to 0.22) 1	-1.40 (-2.07 to -0.9) 2	No data
Rosiglitazone	No data	-0.26 (-1.32 to 0.79) 1	1.16 (0 to 2.33) 1	No data	No data	No data
Antibody 2h6 (deglycosylated)	2.4 (0.1 to 4.7) 2	No data	No data	No data	-0.3 (-1.63 to 1.02) 2	No data
SQ	0.44 (-0.66 to 1.54) 1	0.36 (-0.88 to 1.6) 1	0.22 (-1.05 to 1.49) 1	No data	No data	No data
D1	0 (-1.09 to 1.09) 1	No data	No data	No data	0.52 (-0.28 to 1.32) 1	No data
Ancrod	0.33 (-1.91 to 2.56) 1	No data	No data	No data	No data	No data
Tau379–408	No data	No data	No data	0.31 (0.04 to 0.58) 4	No data	No data
40H-GTS-21	0.3 (-0.58 to 1.19) 1	No data	No data	No data	No data	No data
Antibody 6C6	No data	No data	No data	No data	No data	0.29 (-0.61 to 1.19) 1
Antibody m266	0.06 (-0.36 to 0.48) 2	No data	0.7 (0.16 to 1.24) 1	No data	No data	No data
Clioquinol	0.8 (0.01 to 1.59) 1	-0.63 (-2.07 to 0.81) 1	-0.03 (-1.42 to 1.36) 1	-0.43 (-1.48 to 0.62) 1	No data	2.12 (0.22 to 4.02) 1
Protollin	No data	2.03 (0.74 to 3.32) 1	2.19 (0.83 to 3.54) 1	No data	-2.95 (-4.19 to -1.72) 1	No data
IgG2b	No data	No data	No data	No data	0.26 (-1.34 to 1.87) 1	No data
Antibody NAB61	1.32 (-0.15 to 2.78) 1	0.15 (-0.15 to 0.45) 2	0.14 (-0.31 to 0.58) 2	No data	No data	No data
Antibody Fc fragment	No data	0.13 (-0.52 to 0.78) 3	0.38 (-0.28 to 1.04) 3	No data	No data	No data
Naproxen	No data	0.31 (-0.4 to 1.02) 1	0.18 (-0.44 to 0.8) 2	No data	No data	No data
TAPI-I	No data	0.43 (-0.66 to 1.53) 1	0.04 (-1.05 to 1.12) 1	No data	No data	No data
SMAKEGV	0.23 (-2.39 to 2.86) 2	No data	No data	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Flurbiprofen	0.89 (-0.74 to 2.52) 2	0.21 (0 to 0.42) 8	0.13 (-0.09 to 0.35) 8	No data	No data	No data
Antibody 7b6	0.22 (-1.18 to 1.61) 1	No data	No data	No data	No data	No data
GSM-1	No data	-0.11 (-0.97 to 0.76) 6	1.17 (-0.43 to 2.77) 6	No data	No data	No data
A beta 1-7	0.19 (-1.24 to 1.62) 1	No data	No data	No data	No data	No data
TO 901317	No data	-0.26 (-1.31 to 0.79) 4	0.66 (0.12 to 1.21) 4	No data	No data	No data
celecoxib	0.65 (0.02 to 1.28) 3	0.04 (-0.7 to 0.78) 2	0.03 (-0.89 to 0.96) 2	No data	-0.61 (-1.69 to 0.47) 1	No data
3F1 (FAB fragment)	No data	0.08 (-1.62 to 1.77) 1	0.27 (-1.44 to 1.99) 1	No data	No data	No data
Minocycline	-0.8 1 (-2.59 to 0.96) 2	-0.06 (-0.5 to 0.39) 3	0.13 (-0.3 to 0.56) 3	No data	0.56 (0.07 to 1.06) 3	No data
LY-D	No data	0.63 (-0.47 to 1.74) 3	-0.36 (-1.54 to 0.82) 2	No data	No data	No data
A beta (unspecified length)	1.61 (0.45 to 2.77) 2	No data	No data	No data	-1.41 (-2.58 to -0.24) 2	No data
FK506	No data	No data	0.15 (-0.59 to 0.89) 1	No data	No data	No data
Antibody BBS1	-0.01 (-0.96 to 0.93) 2	-0.92 (-1.93 to 0.09) 2	-0.36 (-1.31 to 0.58) 2	No data	0.48 (0.03 to 0.93) 2	No data
Environmental Enrichment	0.4 (-0.18 to 0.97) 9	-0.45 (-1.72 to 0.82) 5	-0.39 (-1.66 to 0.88) 5	0.1 (-0.7 to 0.9) 1	-0.84 (-1.4 to -0.27) 1	0.35 (-0.49 to 1.19) 1
Antibody BC05	0.96 (0 to 1.93) 1	0.16 (-0.48 to 0.8) 1	-0.32 (-0.99 to 0.35) 1	No data	No data	No data
Gingko Biloba	0.37 (-0.63 to 1.36) 1	0.13 (-0.57 to 0.83) 1	0 (-0.7 to 0.7) 1	No data	No data	No data
MF tricyclic	No data	0.24 (-0.47 to 0.95) 1	0.02 (-0.6 to 0.64) 2	No data	No data	No data
Progesterone	-0.28 (-0.9 to 0.34) 1	No data	No data	1.97 (0.61 to 3.32) 1	No data	No data
Antibody BAM-10	No data	0.05 (-0.33 to 0.42) 1	0.11 (-0.26 to 0.48) 1	No data	No data	No data
Antibody beta-CTF	0.07 (-2.25 to 2.39) 1	No data	No data	No data	No data	No data
DSP-4	0.07 (-1.2 to 1.33) 2	No data	No data	No data	No data	No data
Nimesulide	0.29 (-0.41 to 0.99) 1	0.09 (-0.45 to 0.63) 1	-0.11 (-0.64 to 0.43) 1	No data	No data	No data
Simvastatin	0.14 (-0.48 to 0.76) 1	-0.04 (-0.66 to 0.58) 1	0.06 (-0.56 to 0.68) 1	No data	No data	No data
Losartan	No data	0.16 (-0.41 to 0.72) 1	-0.06 (-0.62 to 0.5) 1	No data	No data	No data
Gamma-secretase site ODN	No data	0.18 (-1.79 to 2.15) 1	-0.09 (-2.05 to 1.87) 1	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
C1q	0.04 (-1.23 to 1.3) 1	No data	No data	No data	No data	No data
Antisense Gamma-site ODN	No data	0.18 (-1.79 to 2.15) 1	-0.11 (-2.07 to 1.86) 1	No data	No data	No data
Pyrrolidine Dithiocarbamate	0.11 (-0.64 to 0.85) 1	0.08 (-0.35 to 0.51) 1	-0.05 (-0.79 to 0.69) 1	No data	0 (-0.38 to 0.38) 1	No data
e64	No data	-0.24 (-1.77 to 1.28) 1	0.3 (-1.23 to 1.84) 1	No data	No data	No data
BDA-410	No data	-0.13 (-1.61 to 1.35) 1	0.18 (-1.3 to 1.66) 1	No data	No data	No data
Donepezil	0.03 (-0.85 to 0.9) 1	No data	No data	No data	No data	No data
GM1 ganglioside	No data	0.04 (-2.08 to 2.15) 2	-0.04 (-2.02 to 1.95) 2	No data	No data	No data
Impoverished housing	0.01 (-0.97 to 0.99) 1	No data	No data	No data	No data	No data
Trolox	0.01 (-0.48 to 0.49) 1	No data	No data	No data	No data	No data
hIGF	No data	No data	No data	0 (-0.6 to 0.61) 2	No data	No data
Egb- 761	-0.01 (-0.49 to 0.48) 1	No data	No data	No data	No data	No data
Aluminium	-1.27 (-2.07 to -0.47) 1	-0.21 (-1.77 to 1.35) 3	0.05 (-1.42 to 1.52) 3	No data	No data	0.26 (-0.24 to 0.75) 2
Rolipram	No data	-0.11 (-0.79 to 0.56) 1	0.11 (-0.77 to 0.99) 1	No data	No data	No data
Paclitaxel	No data	No data	No data	0.03 (-0.67 to 0.72) 2	No data	-4.09 (-9.81 to 1.63) 2
Soybean phosphatidylinositol	No data	No data	No data	No data	No data	-0.05 (-1.82 to 1.73) 1
A beta 25-35	No data	No data	No data	No data	No data	-0.05 (-1.23 to 1.13) 2
A beta 15-24	-0.19 (-0.84 to 0.45) 2	No data	-0.29 (-1.39 to 0.81) 1	No data	No data	0.24 (-0.54 to 1.02) 1
NCX-2216	1.38 (0.51 to 2.26) 2	No data	No data	No data	-1.43 (-1.98 to -0.88) 2	No data
Lipid Neutral Diet	No data	-0.03 (-1.01 to 0.94) 1	-0.14 (-1.12 to 0.83) 1	No data	No data	No data
Sulindac Sulfide	No data	-0.24 (-0.75 to 0.27) 2	0.05 (-0.46 to 0.56) 2	No data	No data	No data
Uch-L1	No data	No data	-0.11 (-0.64 to 0.43) 2	No data	No data	No data
lipoic acid	-0.22 (-0.75 to 0.3) 1	0.07 (-0.66 to 0.8) 1	-0.08 (-0.81 to 0.66) 1	No data	No data	No data
Dexamethasone	-0.51 (-2.9 to 1.89) 2	-0.4 (-1.06 to 0.26) 3	-0.91 (-1.73 to -0.09) 3	-0.12 (-0.95 to 0.71) 2	1.04 (0.39 to 1.7) 1	No data
Intermittent Fasting	No data	-0.23 (-1.18 to 0.71) 1	-0.1 (-1.04 to 0.85) 1	-0.11 (-0.78 to 0.56) 1	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Antibody 2h6	2.29 (1.18 to 3.41) 2	No data	No data	No data	-1.15 (-1.85 to -0.45) 2	No data
Nicotinamide	No data	-0.65 (-1.22 to -0.08) 2	-0.1 (-0.74 to 0.54) 2	0 (-1.11 to 1.11) 2	No data	No data
apoE3 (Lenti-vec tor)	-0.32 (-1.51 to 0.86) 2	No data	-0.11 (-1.15 to 0.93) 2	No data	No data	No data
Antibody 12A11	-0.4 (-1.53 to 0.73) 1	No data	No data	No data	No data	-0.11 (-1 to 0.78) 1
BRI2-del244-266	-0.47 (-1.61 to 0.66) 1	0.03 (-1.09 to 1.15) 1	-0.26 (-1.39 to 0.86) 1	No data	No data	No data
Mild brain trauma	-0.5 (-1.42 to 0.42) 4	-0.24 (-0.77 to 0.29) 2	-0.16 (-0.69 to 0.37) 2	No data	No data	No data
Captopril	-0.7 (-2.05 to 0.65) 2	-0.11 (-0.88 to 0.66) 3	-0.55 (-1.69 to 0.59) 3	No data	No data	No data
Antibody anti-beta 1-16	2.19 (1.09 to 3.29) 1	No data	No data	No data	-0.98 (-1.59 to -0.38) 1	No data
N-benzyloxycarbonyl-valine-leucine-		-0.54 (-1.99 to 0.92) 1	-0.03 (-1.41 to 1.36) 1	No data	No data	No data
A beta 1-9	12.12 (5.18 to 19.05) 1	0.4 (-0.81 to 1.6) 1	0.28 (-0.91 to 1.48) 1	No data	-1.61 (-2.7 to -0.52) 1	No data
Scolopamine Hydorbromide	No data	-0.44 (-1.28 to 0.39) 1	-0.3 (-1.27 to 0.67) 1	No data	No data	No data
Sodium butyrate	No data	-0.38 (-1.09 to 0.32) 1	0.24 (-0.45 to 0.94) 1	-0.85 (-1.45 to -0.25) 1	No data	No data
A beta 16-20	0.5 (-0.82 to 1.82) 1	No data	No data	No data	-0.89 (-2.34 to 0.55) 1	-0.96 (-2.4 to 0.47) 1
Zinc deficiency	-0.5 (-0.86 to -0.13) 1	No data	No data	No data	No data	No data
Metrifonate	0.31 (-0.35 to 0.97) 1	-0.96 (-1.65 to -0.26) 1	-1.12 (-1.83 to -0.41) 1	No data	No data	No data
High Cholesterol	-0.9 (-2.28 to 0.48) 4	-0.05 (-1 to 0.91) 3	-0.2 (-0.64 to 0.24) 3	No data	No data	No data
Roscovitine	No data	No data	-0.56 (-1.7 to 0.57) 2	No data	No data	No data
Dicyclomine	-0.78 (-1.48 to -0.08) 1	-1.21 (-2.48 to 0.07) 1	-0.75 (-1.6 to 0.11) 1	-0.46 (-0.82 to -0.09) 1	No data	No data
Typical Western Diet	-0.66 (-1.53 to 0.22) 1	-0.59 (-1.58 to 0.4) 1	-0.55 (-1.54 to 0.44) 1	No data	No data	No data
KMI-358	No data	-0.58 (-2.05 to 0.89) 1	-0.7 (-2.2 to 0.8) 1	No data	No data	No data
3-Nitropropionic acid (3NP)	No data	-0.64 (-2.09 to 0.82) 3	No data	No data	No data	No data
B-vitamin Deprivation	-0.77 (-1.4 to -0.15) 2	-0.96 (-1.5 to -0.42) 2	-0.21 (-0.72 to 0.3) 2	No data	No data	No data
apoE4(Lenti-vec to r)	-0.68 (-1.37 to 0.02) 5	No data	-0.77 (-1.93 to 0.39) 2	No data	No data	No data
2-deoxyglucose(2DG)	No data	-0.73 (-2.24 to 0.78) 3	No data	No data	No data	No data

Drug	Plaque area SMD Effect size (95 % CI) and N	Amyloid beta 40 SMD Effect size (95 % CI) and N	Amyloid beta 42 SMD Effect size (95 % CI) and N	Tau SMD Effect size (95 % CI) and N	Cellular infiltrates SMD Effect size (95 % CI) and N	Neurodegeneration SMD Effect size (95 % CI) and N
Antibody 2286	5.23 (-0.01 to 10.47) 1	No data	No data	No data	-0.9 (-1.73 to -0.07) 1	No data
Kainic acid	No data	-0.87 (-2.41 to 0.67) 3	No data	No data	No data	No data
A beta 16-22	-1.24 (-2.37 to -0.1) 1	No data	No data	No data	-0.44 (-1.75 to 0.86) 1	No data
Sucrose Sweetened Water	-1.92 (-3.26 to -0.58) 1	-0.71 (-1.49 to 0.06) 1	-0.82 (-1.63 to 0) 1	No data	No data	No data
Tranexamic acid	-0.43 (-2.62 to 1.76) 1	No data	No data	No data	-1.99 (-4.88 to 0.89) 1	No data
Insulin	No data	-1.06 (-2.58 to 0.46) 3	No data	No data	No data	No data
SAP protein	-1.29 (-2.83 to 0.24) 1	No data	No data	No data	No data	No data
iPF2a-11 (IsoP)	-1.29 (-2.46 to -0.12) 1	-1.65 (-3.29 to 0) 1	-1.61 (-3.25 to 0.03) 1	No data	No data	No data
M3D6	No data	No data	No data	No data	-2.41 (-5.53 to 0.71) 3	No data
Isolation Stress	-6.96 (-11.07 to -2.85) 1	No data	No data	No data	No data	-2.61 (-4.05 to -1.18) 1

Key: Significant improvement | Non. sig. improvement | Non. sig. worsening | Significant worsening

Table 6.3: I summarised the effect of interventions across the six principle pathological outcomes. Effect size estimates provided are given in terms of standardised mean difference alongside 95% confidence limits and number of experiments. Each estimate is assigned a heat map colour as explained in the key.

6.3.2 Heat map for neurobehavioural outcomes

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Amyloid beta-12-28P	no data	no data	2.86 (1.61 to 4.11) 1	2.86 (1.61 to 4.11) 1
A beta 36-42	2.11 (0.32 to 3.89) 1	2.25 (0.9 to 3.61) 1	no data	2.2 (1.12 to 3.28) 1
A beta 1-11	1.52 (0.24 to 2.8) 1	2.73 (1.45 to 4.01) 1	no data	2.13 (1.22 to 3.03) 1
Blueberry supplementation	no data	no data	1.9 (-0.53 to 4.33) 1	1.9 (-0.53 to 4.33) 1
Testosterone	no data	no data	1.81 (0.38 to 3.25) 1	1.81 (0.38 to 3.25) 1
PBT2	2.01 (1.16 to 2.86) 2	1.35 (0.51 to 2.2) 2	no data	1.68 (1.08 to 2.28) 2
Antibody 2h6	no data	no data	1.66 (-0.08 to 3.4) 1	1.66 (-0.08 to 3.4) 1
Antibody m266	no data	no data	1.65 (0.51 to 2.78) 5	1.65 (0.51 to 2.78) 5
Nogo-66 receptor -ecto-Fc	no data	no data	1.62 (0.44 to 2.79) 1	1.62 (0.44 to 2.79) 1
A beta 1-15	0.98 (-0.41 to 2.37) 3	1.61 (-0.19 to 3.42) 3	2.46 (0.1 to 4.82) 1	1.6 (0.2 to 3.01) 4
Resveratrol	no data	no data	1.58 (0.29 to 2.88) 1	1.58 (0.29 to 2.88) 1
Nobiletin	no data	no data	1.5 (0.35 to 2.65) 1	1.5 (0.35 to 2.65) 1
BDA-410	no data	no data	1.43 (0 to 2.86) 2	1.43 (0 to 2.86) 2

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Antibody 2h6	no data	no data	1.41 (-0.36 to 3.19) 1	1.41 (-0.36 to 3.19) 1
Physostigmine	no data	no data	1.38 (0.51 to 2.25) 3	1.38 (0.51 to 2.25) 3
G-CSF	1.37 (-0.09 to 2.82) 1	no data	no data	1.37 (-0.09 to 2.82) 1
TO901317	no data	no data	1.36 (0.31 to 2.42) 1	1.36 (0.31 to 2.42) 1
Neprilysin	0.88 (-0.16 to 1.92) 1	1.41 (0.62 to 2.2) 2	no data	1.36 (0.52 to 2.19) 2
Garlic extract	0.79 (0.14 to 1.44) 2	2.67 (1.56 to 3.77) 2	1.16 (-0.67 to 2.98) 2	1.32 (0.33 to 2.31) 2
antibody 10d5	1.32 (0.39 to 2.24) 1	no data	no data	1.32 (0.39 to 2.24) 1
epigallocatechin-3-	no data	no data	1.29 (0.57 to 2.01) 2	1.29 (0.57 to 2.01) 2
NAP	no data	1.28 (0.61 to 1.94) 1	no data	1.28 (0.61 to 1.94) 1
ST1571	1.27 (-0.19 to 2.74) 1	no data	no data	1.27 (-0.19 to 2.74) 1
Rosiglitazone	no data	no data	1.26 (0.42 to 2.1) 1	1.26 (0.42 to 2.1) 1
AF267B	0.71 (-0.41 to 1.83) 1	1.57 (0.7 to 2.43) 1	no data	1.25 (0.56 to 1.93) 1
e64	no data	no data	1.2 (0.19 to 2.2) 1	1.2 (0.19 to 2.2) 1
Lenti-siBACE1-6	0.41 (-0.85 to 1.67) 1	1.79 (0.65 to 2.93) 1	no data	1.17 (0.33 to 2.02) 1

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Memapsin 2	0.67 (-0.26 to 1.61) 2	1.72 (-0.58 to 4.02) 2	no data	1.12 (0.01 to 2.24) 2
Lipoic acid	0.99 (-0.12 to 2.1) 1	1.55 (0.69 to 2.41) 1	0.79 (0.02 to 1.56) 1	1.1 (0.59 to 1.61) 1
Gingko Biloba	0.9 (-0.15 to 1.95) 1	1.16 (0.53 to 1.79) 1	no data	1.09 (0.55 to 1.63) 1
Retinoic-acid	0.84 (-0.37 to 2.04) 1	1.35 (0.04 to 2.66) 1	no data	1.07 (0.19 to 1.96) 1
Antibody D-2H6	no data	no data	1.06 (-0.11 to 2.23) 3	1.06 (-0.11 to 2.23) 3
FK506	no data	no data	1.05 (0.33 to 1.76) 1	1.05 (0.33 to 1.76) 1
Glatiramer acetate	1.04 (-0.15 to 2.24) 1	no data	no data	1.04 (-0.15 to 2.24) 1
PAZ-417	no data	no data	1.02 (0.35 to 1.69) 4	1.02 (0.35 to 1.69) 4
Naproxen	no data	1.02 (-0.04 to 2.08) 1	no data	1.02 (-0.04 to 2.08) 1
Ibuprofen	1.66 (0.11 to 3.21) 1	0.79 (0.32 to 1.26) 3	1.41 (0.62 to 2.19) 1	1 (0.61 to 1.39) 3
T cells	no data	no data	0.95 (0.51 to 1.39) 3	0.95 (0.51 to 1.39) 3
Environmental Enrichment	0.76 (0.35 to 1.17) 6	0.79 (0.22 to 1.36) 7	1.37 (0.96 to 1.78) 7	0.94 (0.7 to 1.19) 9
Antibody 2286	no data	no data	0.93 (-0.33 to 2.18) 1	0.93 (-0.33 to 2.18) 1
Leuprolide	no data	no data	0.92 (-0.28 to 2.11) 1	0.92 (-0.28 to 2.11) 1

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Clioquinol	1.43 (0.29 to 2.57) 1	0.52 (-0.49 to 1.53) 1	no data	0.92 (0.16 to 1.67) 1
DAPT	no data	no data	0.86 (0.13 to 1.59) 5	0.86 (0.13 to 1.59) 5
Nicotine	0.26 (-0.15 to 0.68) 3	1.6 (1.13 to 2.07) 3	no data	0.86 (0.54 to 1.17) 3
Grape Polyphenolics	0.98 (-0.25 to 2.2) 1	0.82 (0.07 to 1.57) 1	no data	0.86 (0.22 to 1.51) 1
CNI-1493	no data	no data	0.84 (0.25 to 1.42) 1	0.84 (0.25 to 1.42) 1
Nicotinamide	0.29 (-0.7 to 1.28) 1	1.39 (0.6 to 2.19) 1	0.64 (-0.08 to 1.37) 1	0.83 (0.35 to 1.3) 1
Caffeine	0.98 (0.3 to 1.66) 1	0.76 (0.29 to 1.23) 1	no data	0.83 (0.44 to 1.22) 1
Pyrrolidine	0.47 (-0.29 to 1.22) 1	1.23 (0.41 to 2.05) 1	no data	0.81 (0.26 to 1.37) 1
Antibody BBS1	no data	no data	0.8 (-0.21 to 1.8) 2	0.8 (-0.21 to 1.8) 2
TSG	no data	0.62 (0.2 to 1.03) 4	0.98 (0.22 to 1.74) 4	0.78 (0.27 to 1.3) 4
LDN-57444	no data	no data	0.75 (0.09 to 1.41) 1	0.75 (0.09 to 1.41) 1
Picrotoxin	no data	1.62 (0.24 to 3) 1	0.13 (-1.01 to 1.26) 1	0.73 (-0.15 to 1.6) 1
A beta 1-42	0.63 (0.32 to 0.94) 15	0.88 (0.53 to 1.24) 13	0.62 (-0.14 to 1.38) 7	0.72 (0.44 to 1) 23
MF tricyclic	no data	0.71 (-0.32 to 1.75) 1	no data	0.71 (-0.32 to 1.75) 1

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Rolipram	0.43 (-0.38 to 1.24) 1	0.59 (0.01 to 1.17) 1	0.83 (0.37 to 1.29) 4	0.7 (0.37 to 1.03) 5
Pomegranate juice	0.89 (0.4 to 1.38) 1	0.3 (-0.36 to 0.96) 1	no data	0.68 (0.29 to 1.08) 1
Uch-L1	no data	no data	0.66 (0.14 to 1.19) 2	0.66 (0.14 to 1.19) 2
Antibody BAM-10	no data	0.66 (-0.12 to 1.44) 1	no data	0.66 (-0.12 to 1.44) 1
Cerebrolysin	0.66 (0.17 to 1.14) 3	no data	no data	0.66 (0.17 to 1.14) 3
Caloric restriction	0.62 (-0.07 to 1.31) 3	0.72 (0.28 to 1.16) 2	no data	0.61 (0.29 to 0.92) 4
Progesterone	no data	no data	0.6 (-0.56 to 1.76) 2	0.6 (-0.56 to 1.76) 2
Antibody 20.1 (monoclonal)	no data	no data	0.59 (-0.43 to 1.62) 2	0.59 (-0.43 to 1.62) 2
Intermittent Fasting	0.54 (-0.12 to 1.2) 3	0.2 (-0.6 to 1.01) 2	no data	0.49 (-0.06 to 1.04) 4
NGF	no data	no data	0.48 (0.16 to 0.81) 2	0.48 (0.16 to 0.81) 2
Insulin-like Growth factor 1	0.48 (-0.33 to 1.3) 1	no data	no data	0.48 (-0.33 to 1.3) 1
Scyllo-cyclohexanehexol	0.41 (-0.1 to 0.93) 7	0.75 (-0.37 to 1.86) 1	no data	0.47 (0 to 0.94) 7
Valsartan	0.7 (0.03 to 1.37) 4	0.24 (-0.43 to 0.91) 2	no data	0.47 (0 to 0.94) 4
Exercise	0.71 (-0.09 to 1.51) 2	0.24 (-0.56 to 1.04) 4	0.44 (-0.12 to 1) 4	0.44 (0.01 to 0.86) 8

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
DSP-4	no data	no data	0.44 (-0.38 to 1.26) 2	0.44 (-0.38 to 1.26) 2
Antibody NAB61	0.84 (0.08 to 1.59) 1	0.32 (-0.09 to 0.74) 1	no data	0.44 (0.08 to 0.81) 1
Lithium	1.67 (0.68 to 2.65) 1	-0.04 (-0.85 to 0.76) 1	0.03 (-0.85 to 0.9) 1	0.41 (-0.17 to 1) 2
Donepezil	0.44 (-0.02 to 0.9) 4	0.25 (-0.29 to 0.8) 4	0.71 (-0.03 to 1.44) 3	0.41 (0.1 to 0.72) 7
Valproic acid	0.36 (0 to 0.72) 1	0.51 (0 to 1.03) 1	no data	0.41 (0.11 to 0.7) 1
Estrogen	0.36 (-0.08 to 0.8) 3	0.06 (-0.35 to 0.46) 3	0.51 (0.28 to 0.75) 4	0.4 (0.15 to 0.64) 5
Epi-cyclohexanehexol	0.36 (-0.31 to 1.04) 3	0.3 (-0.78 to 1.38) 1	no data	0.35 (-0.23 to 0.92) 3
Paroxetine	0.71 (-0.2 to 1.62) 1	-0.05 (-0.92 to 0.83) 1	no data	0.32 (-0.31 to 0.95) 1
Simvastatin	0.43 (-0.01 to 0.88) 1	0.35 (-0.09 to 0.79) 1	0.14 (-0.3 to 0.58) 1	0.31 (0.05 to 0.56) 1
Galantamine	0.36 (-0.1 to 0.82) 4	0.27 (-0.24 to 0.77) 4	no data	0.31 (-0.11 to 0.73) 4
Antibody 1560	0.06 (-0.92 to 1.03) 2	0.82 (-0.32 to 1.96) 2	-0.32 (-1.3 to 0.67) 2	0.3 (-0.21 to 0.81) 2
MDVFMKGLSMAKE	0.3 (-0.84 to 1.44) 1	no data	no data	0.3 (-0.84 to 1.44) 1
A beta 1-30	no data	no data	0.29 (-0.66 to 1.24) 4	0.29 (-0.66 to 1.24) 4
Memantine	0.41 (0.04 to 0.78) 5	0.26 (-0.15 to 0.67) 4	0.24 (-0.45 to 0.93) 4	0.28 (-0.03 to 0.58) 9

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Bacopa Monniera	no data	no data	0.27 (-0.19 to 0.72) 2	0.27 (-0.19 to 0.72) 2
Rivastigmine	0.39 (-0.38 to 1.17) 2	0.09 (-0.55 to 0.73) 2	no data	0.21 (-0.28 to 0.7) 2
Flurbiprofen	no data	0.19 (-0.17 to 0.56) 2	no data	0.19 (-0.17 to 0.56) 2
PBD150	0.12 (-1.16 to 1.41) 1	0.12 (-0.93 to 1.17) 1	0.25 (-0.62 to 1.11) 4	0.18 (-0.41 to 0.77) 5
Metyrapone	no data	no data	0.14 (-0.61 to 0.89) 1	0.14 (-0.61 to 0.89) 1
Minocycline	0.13 (-1.75 to 2.01) 2	no data	no data	0.13 (-1.75 to 2.01) 2
Learning	0.17 (-0.39 to 0.73) 7	0.08 (-0.25 to 0.41) 8	no data	0.12 (-0.17 to 0.41) 15
Typical Western Diet	0.12 (-0.86 to 1.09) 1	no data	no data	0.12 (-0.86 to 1.09) 1
Lipid Neutral Diet	0.11 (-0.87 to 1.08) 1	no data	no data	0.11 (-0.87 to 1.08) 1
High Fat diet	0.26 (-0.69 to 1.22) 1	0.4 (-0.57 to 1.36) 1	-0.15 (-0.82 to 0.53) 1	0.09 (-0.39 to 0.57) 1
Aluminium	0.26 (-0.72 to 1.25) 1	0.01 (-0.68 to 0.71) 1	no data	0.09 (-0.47 to 0.66) 1
Metrifonate	0.03 (-0.5 to 0.55) 1	no data	no data	0.03 (-0.5 to 0.55) 1
celecoxib	no data	no data	-0.04 (-0.43 to 0.35) 3	-0.04 (-0.43 to 0.35) 3
EFRH	-0.05 (-0.64 to 0.55) 3	no data	no data	-0.05 (-0.64 to 0.55) 3

Drug	Acquisition SMD Effect size (95 % CI) and N	Probe SMD Effect size (95 % CI) and N	Other SMD Effect size (95 % CI) and N	Combined SMD Effect size (95 % CI) and N
Tau379–408	no data	no data	-0.22 (-1.02 to 0.59) 1	-0.22 (-1.02 to 0.59) 1
a beta 1-16	no data	no data	-0.23 (-1.76 to 1.3) 1	-0.23 (-1.76 to 1.3) 1
B-vitamin Deprivation	-0.25 (-1.16 to 0.65) 1	no data	no data	-0.25 (-1.16 to 0.65) 1
Mild brain trauma	-0.26 (-1.02 to 0.49) 2	no data	no data	-0.26 (-1.02 to 0.49) 2
DHA	-0.26 (-1.24 to 0.72) 1	no data	no data	-0.26 (-1.24 to 0.72) 1
impoverished housing	no data	-0.56 (-1.58 to 0.46) 1	-0.12 (-1.5 to 1.27) 1	-0.4 (-1.22 to 0.42) 1
Pioglitazone	-0.22 (-1.61 to 1.17) 1	-0.65 (-1.51 to 0.2) 1	no data	-0.54 (-1.26 to 0.19) 1
Dicyclomine	0.13 (-1.03 to 1.29) 1	-1.14 (-2.03 to -0.24) 1	no data	-0.67 (-1.37 to 0.04) 1
Sucrose Sweetened Water	-0.8 (-1.91 to 0.3) 1	-1.25 (-2.09 to -0.42) 1	-0.37 (-1.1 to 0.36) 1	-0.76 (-1.26 to -0.27) 1
Isolation Stress	no data	no data	-1.07 (-1.9 to -0.23) 1	-1.07 (-1.9 to -0.23) 1

Key: Significant improvement | Non. sig. improvement | Non. sig. worsening | Significant worsening

Table 6.4: Summary estimates of effect (standardised effect size), 95% confidence limits and number of experiments for each intervention behaviourally tested. Each estimate is assigned a heat map colour as explained in the key.

6.4 Interpreting intervention analyses

6.4.1 Summary of findings

Overall I identified 357 interventions tested in transgenic mouse models of AD. Few interventions were tested on more than one occasion and only 4% (16 of 357) report outcomes in 5 publications or more. This limits the reliability of individual intervention estimates and also prevents us performing dose response analyses. Nevertheless, I was able to examine amyloid fragments in further detail where I identified that gene immunisation was generally more effective at reducing pathological outcomes than peptide immunisation and that N terminal fragments were just as effective as full length amyloid beta 1-42.

6.4.2 Implications of findings

While the breadth of interventions tested is extensive, the depth of knowledge on any specific intervention is limited. From the data identified, there are only a handful of interventions where preclinical transgenic studies provide sufficient data for reliable estimates. Considering that most of these interventions appear to work, the field may benefit from exploring how much data remains unpublished, both collectively and specifically for each outcome measure. While Chapter 7 investigates missing negative or neutral data in further detail, the reader should bear in mind that positive studies may also never reach publication.

Chapter 7: Study quality and publication bias

Our understanding of how study quality items or publication bias may influence our preclinical trials in AD is relatively unknown. This chapter assesses the impact of aggregate study quality and individual study quality items on pathological and neurobehavioural outcomes. I subsequently assess an additional study quality item to examine whether the presence of a wild type group impacts on behavioural outcomes. Data are assessed for the presence of publication bias through Egger regression, Funnel plotting and 'Trim and fill' techniques.

7.1 Study quality items

7.1.1 Total Study quality Score

I performed a stratified analysis to assess the potential impact of aggregate study quality on pathology and behaviour overall, and for individual outcomes (see Table 7.1 for overview). For pathological outcomes, I observed that aggregate study quality (defined by the individual components of blinding, randomisation, conflict of interest, compliance with animal welfare legislation) accounted for a significant proportion of the observed heterogeneity (χ^2=142, 725 observations, p<0.01, Table 7.1) however there was no clear relationship between study quality and effect size. Similarly, stratifying neurobehavioral summary data accounted for a significant proportion of the observed heterogeneity but a clear relationship could not be defined (χ^2=10.4, p<0.01, 259 observations, Table 7.1).

I observed that stratifying individual outcome measures by overall study quality score could explain a significant proportion of the heterogeneity in four out of six of the main pathological outcomes (See Table 7.1 and Figure 7.1 for overview of individual outcomes). Although stratifications proved significant regarding plaque burden (χ^2=110, p<0.01, Figure 7.1a), amyloid beta 40 (χ^2=9.27, p<0.01, Figure 7.1b) amyloid beta 42 (χ^2=23.3, Figure p<0.01, 7.1c), tau neurofibrillary tangles (χ^2=13.4, p<0.01, Figure 7.1d) it was not possible to identify clear relationships between study quality and effect size. Stratifying results from cell infiltrates did however suggest a relationship, with greater effect sizes associated with higher study quality (χ^2=129, p<0.01, Figure 7.1e). Stratification of neurodegeneration outcomes did not explain a significant proportion of the heterogeneity.

For individual behavioural outcomes, stratifying outcomes for the acquisition phase of the MWM by study quality suggested a modest inverse relationship between study quality and effect size but this did not account for a significant proportion of heterogeneity (p<0.01, Figure 7.1g).I observed that for outcomes from the probe phase of the MWM, there was an inverse relationship between study quality and intervention efficacy (χ^2=13.8, p<0.01, Figure 7.1h). As other neurobehavioral studies had fewer studies, I combined data from the Fear conditioning, RAWM, NORT, and the Y and T maze to increase power. However this did not account for a significant proportion of the observed heterogeneity (123 observations, χ^2= 6.4, p<0.01, Figure 7.1I).

Outcome measure	Aggregate Study Quality					Combined
	0	1	2	3	4	
Plaque burden* (antibody stained)	1.07 SD (0.85 to 1.29) **91**	0.79 SD (0.60 to 0.98) **151**	0.89 SD (0.7 to 1.08) **99**	1.67 SD (1.25 to 2.08) **35**	1.24 SD (0.52 to 1.97) **2**	0.98 SD (0.87 to 1.1) **378 (χ 2= 110)**
Amyloid beta 40	1 SD (0.7 to 1.29) **68**	0.72 SD (0.56 to 0.87) **211**	0.45 SD (0.27 to 0.62) **81**	0.73 SD (0.34 to 1.12) **27**	-0.13 SD (-0.78 to 0.53) **1**	0.68 SD (0.57 to 0.79) **388 (χ 2= 9.27)**
Amyloid beta 42*	1.21 SD (0.92 to 1.5) **70**	0.66 SD (0.51 to 0.8) **201**	0.72 SD (0.51 to 0.93) **81**	0.87 SD (0.51 to 1.22) **36**	-0.24 SD (-0.9 to 0.43) **1**	0.78 SD (0.67 to 0.88) **389 (χ 2= 23.3)**
NFT*	0.49 SD (0.19 to 0.78) **15**	0.57 SD (0.32 to 0.83) **52**	0.64 SD (0.09 to 1.2) **6**	0.73 SD (0.31 to 1.14) **11**	No studies	0.55 SD (0.38 to 0.72) **84 (χ 2= 13.4)**
Cell infiltrates*	0.04 SD (-0.48 to 0.56) **20**	0.34 SD (-0.01 to 0.7) **30**	0.23 SD (-0.3 to 0.77) **27**	1.53 SD (0.64 to 2.41) **12**	No studies	0.4 SD (0.13 to 0.68) **89 (χ 2= 129)**
Neurodegeneration	0.54 SD (-0.25 to 1.33) **7**	0.99 SD (0.6 to 1.38) **24**	0.94 SD (0.64 to 1.23) **25**	0.91 SD (0.21 to 1.62) **8**	No studies	0.91 SD (0.69 to 1.12) **64 (χ 2= 2.8)**
Total Pathology	0.96 SD (0.8 to 1.13) **146**	0.72 SD (0.62 to 0.82) **348**	0.65 SD (0.52 to 0.78) **164**	1.09 SD (0.82 to 1.37) **65**	0.66 SD (0.35 to 0.97) **2**	0.78 SD (0.71 to 0.85) **725 (χ 2=142)**
Acquisition phase of MWM	0.52 SD (0.3 to 0.73) 25	0.59 SD (0.41 to 0.77) 50	0.42 SD (0.27 to 0.57) 29	0.46 SD (0.22 to 0.69) 26	No studies	0.49 SD (0.41 to 0.58) 130 **(χ 2= 1.59)**
Probe phase of MWM*	0.72 SD (0.4 to 1.03) **24**	0.84 SD (0.6 to 1.07) **47**	0.4 SD (0.22 to 0.58) **26**	0.41 SD (0.08 to 0.75) **16**	No studies	0.63 SD (0.5 to 0.76) **113 (χ 2= 13.8)**
Other NBS studies*	0.78 SD (0.51 to 1.05) **28**	0.69 SD (0.49 to 0.89) **39**	0.56 SD (0.34 to 0.79) **38**	1.05 SD (0.63 to 1.46) **18**	No studies	0.72 SD (0.59 to 0.84) 123 (χ 2= 6.4)
Total Behaviour	0.65 SD (0.49 to 0.82) **62**	0.70 SD (0.57 to 0.84) **86**	0.46 SD (0.33 to 0.58) **67**	0.64 SD (0.44 to 0.85) **44**	No studies	0.61 SD (0.54 to 0.69) **259 (χ 2= 10.4)**

Table 7.1: I stratified outcomes to identify whether there was an association between effect size and overall study quality. For each outcome, summary estimates are provided regarding effect size, 95% confidence limits and number of experiments alongside chi squared value (χ^2), *represents stratifications which accounted for a significant proportion of the observed heterogeneity.

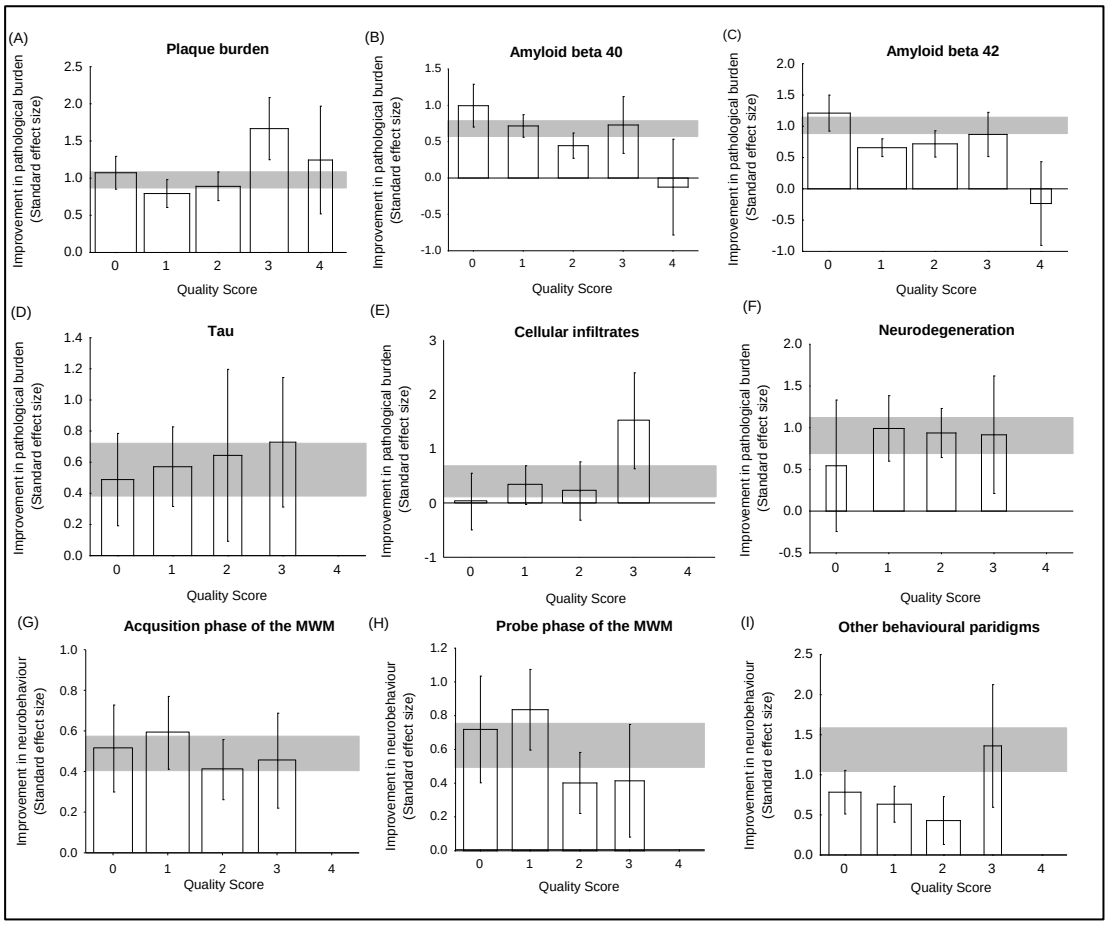


Figure 7.1: I stratified outcomes to identify whether there was an association between effect size and overall study quality. For each outcome, grey bar represents 95% confidence limit (CI) of global estimate, error bars represent 95% CI of summary estimates and bar width represents the log of the number of animals.

7.1.2 Blinded assessment of outcome

I performed a stratified analysis in order to assess the impact of blinded assessment of outcome on pathological and behaviour overall, and for individual outcomes (see Table 7.2 for summary and Figure 7.2 for overview of individual outcomes). Stratification of pathological and neurobehavioral outcomes did not account for a significant proportion of the observed heterogeneity (725 observations and 259 observations respectively, Table 7.2).

I observed that stratifying results by the presence of blinding could explain a significant proportion of the heterogeneity in one of the six main pathological outcomes (See table 7.2 for overview). For cell infiltrates, the presence of blinding was associated with higher estimates of efficacy (0.55 SD [95% CI -0.11 to 1.22] vs. 0.35 SD [0.08 to 0.61], Figure 7.2e). I did not identify any individual behavioural outcome measure where stratifying data by the presence of blinding accounted for a significant proportion of the observed heterogeneity.

Outcome measure	Blinded assessment of outcome		Combined	Critical χ^2 =6.63 df=1
	Yes	No		
Plaque burden* (antibody stained)	1.15 SD (0.89 to 1.4) **93**	0.91 SD (0.79 to 1.04) **285**	0.98 SD (0.87 to 1.1) **378**	χ^2 = 0.15 **Non Sig.**
Amyloid beta 40	0.46 SD (0.26 to 0.66) **68**	0.75 SD (0.63 to 0.88) **320**	0.68 SD (0.57 to 0.79) **388**	χ^2 = 5.17 **Non Sig.**
Amyloid beta 42	0.58 SD (0.39 to 0.77) **82**	0.85 SD (0.72 to 0.97) **307**	0.78 SD (0.67 to 0.88) **389**	χ^2 = 5.88 **Non Sig.**
NFT*	0.89 SD (0.3 to 1.48) **14**	0.51 SD (0.33 to 0.69) **70**	0.55 SD (0.38 to 0.72) **84**	χ^2 = 3.16 **Non Sig.**
Cell infiltrates*	0.55 SD (-0.11 to 1.22) **28**	0.35 SD (0.08 to 0.61) **61**	0.4 SD (0.13 to 0.68) **89**	χ^2= 12.2 **Sig**
Neurodegeneration	0.80 SD (0.51 to 1.1) **22**	1 SD (0.7 to 1.3) **42**	0.91 SD (0.69 to 1.12) **64**	χ^2 = 0.11 **Non Sig.**
Total Pathology	0.72 SD (0.56 to 0.88) **139**	0.8 SD (0.72 to 0.87) **586**	0.78 SD (0.71 to 0.85) **725**	χ^2= 0.00 **Non Sig**
Acquisition phase of MWM	0.39 SD (0.14 to 0.64) **18**	0.51 SD (0.42 to 0.61) **112**	0.49 SD (0.41 to 0.58) **130**	χ^2 = 0.73 **Non Sig.**
Probe phase of MWM	0.36 SD (0 to 0.71) **15**	0.67 SD (0.53 to 0.81) **98**	0.63 SD (0.5 to 0.76) **113**	χ^2 = 3 **Non Sig.**
Other neurobehavioural studies	0.88 SD (0.63 to 1.13) **19**	0.68 SD (0.54 to 0.82) **104**	0.72 SD (0.59 to 0.84) **123**	χ^2= 4.41 **Non Sig.**
Total Behaviour	0.58 SD (0.4 to 0.77) **37**	0.66 SD (0.53 to 0.70) **222**	0.61 SD (0.54 to 0.69) **259**	χ^2= 0.00 **Non Sig**

Table 7.2: I stratified outcomes to identify whether there was an association between effect size and blinded assessment of outcome. For each outcome, summary estimates are provided regarding effect size, 95% confidence limits and number of experiments alongside chi squared value (χ^2), *represents stratifications which accounted for a significant proportion of the observed heterogeneity.

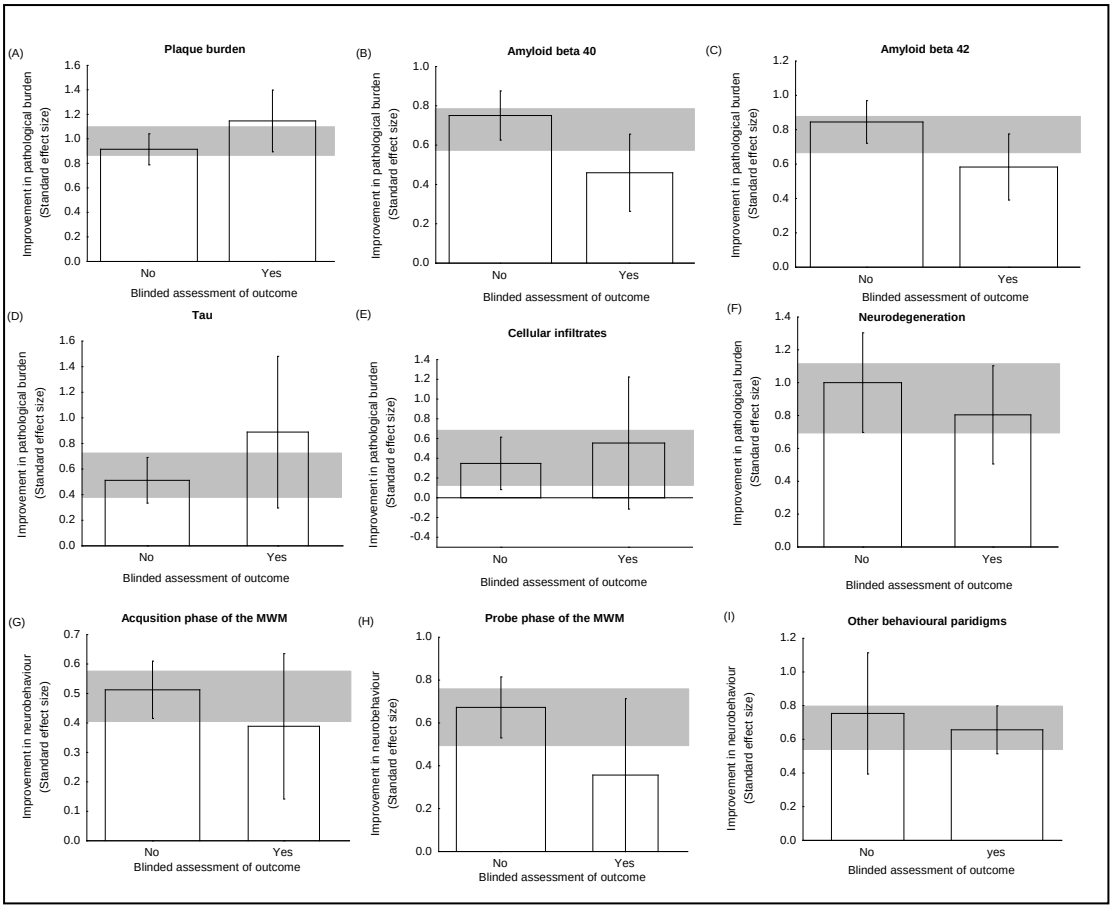


Figure 7.2: I stratified outcomes to identify whether there was an association between effect size and blinded assessment of outcome. For each outcome, grey bar represents 95% confidence limit (CI) of global estimate, error bars represent 95% CI of summary estimates and bar width represents the log of the number of animals.

7.1.3 Random allocation to group

I performed a stratified analysis in order to assess the impact of random allocation to group on pathological and behaviour overall, and for individual outcomes (see Table 7.3 and Figure 7.3 for overview of individual outcomes). For pathological outcomes, I observed that stratifying data according to whether experimental cohort were randomised or not accounted for a significant proportion of the observed heterogeneity (χ^2=41.2, p<0.01, 725 observations, Table 7.3). Stratifying neurobehavioral summary data did not account for a significant proportion of the observed heterogeneity (259 observations, Table 7.3).

I observed that stratifying data according to the presence of randomisation could explain a significant proportion of heterogeneity in two individual pathological outcomes, plaque burden and cell infiltrates. For plaque burden marginally smaller estimates of effect size were obtained from randomised experiments compared to non-randomised experiments (0.96 SD [0.70 to 1.21] vs. 0.99 SD [0.86 to 1.12], Figure7.3a). For cell infiltrates the converse was true where higher estimates of effect size were found in randomised experiments (Figure 7.3e). For neurobehavioral studies the combined data from Fear conditioning, RAWM, NORT, stratification by random allocation to group did not account for a significant proportion of the observed heterogeneity.

Outcome measure	Random Allocation to group		Combined	Critical χ^2 =6.63 df=1
	Yes	No		
Plaque burden* (antibody stained)	0.96 SD (0.7 to 1.21) **55**	0.99 SD (0.86 to 1.12) **323**	0.98 SD (0.87 to 1.1) **378**	χ^2 = 24.98 **Sig.**
Amyloid beta 40	0.69 SD (0.41 to 0.97) **54**	0.68 SD (0.56 to 0.79) **334**	0.68 SD (0.57 to 0.79) **388**	χ^2 = 4.53 **Non sig.**
Amyloid beta 42	1.06 SD (0.74 to 1.38) **55**	0.73 SD (0.62 to 0.84) **334**	0.78 SD (0.67 to 0.88) **389**	χ^2 = 1.09 **Non sig.**
NFT*	0.51 SD (0.19 to 0.83) **17**	0.56 SD (0.36 to 0.76) **67**	0.55 SD (0.38 to 0.72) **84**	χ^2 = 1.02 **Non sig.**
Cell infiltrates*	1.03 SD (0.23 to 1.84) **12**	0.3 SD (0.02 to 0.58) **77**	0.4 SD (0.13 to 0.68) **89**	χ^2 = 90.8 **Sig.**
Neurodegeneration	0.67 SD (0.27 to 1.08) **15**	0.97 SD (0.73 to 1.22) **49**	0.91 SD (0.69 to 1.12) **64**	χ^2 = 4.14 **Non sig.**
Total pathology	0.84 SD (0.65 to 1.02) 114	0.77 SD (0.7 to 0.85) 611	0.78 SD (0.71 to 0.85) **725**	χ^2 = 41.15 **Sig**
Acquisition phase of MWM	0.43 SD (0.28 to 0.59) **41**	0.52 SD (0.41 to 0.63) **89**	0.49 SD (0.41 to 0.58) **130**	χ^2 = 0.57 **Non sig.**
Probe phase of MWM	0.44 SD (0.23 to 0.65) **34**	0.71 SD (0.55 to 0.88) **79**	0.63 SD (0.5 to 0.76) **113**	χ^2 = 3.86 **Non sig.**
Other neurobehavioural studies	0.60 SD (0.30 to 0.90) **23**	0.74 SD (0.60 to 0.88) **100**	0.72 SD (0.59 to 0.84) **123**	χ 2 = 0.13 **Non. sig**
Total Behaviour*	0.51 SD (0.36 to 0.66) **62**	0.64 SD (0.56 to 0.73) **197**	0.61 SD (0.54 to 0.69) **259**	χ^2 = 6.27 **Non. sig**

Table 7.3: I stratified outcomes to identify whether there was an association between effect size and random allocation to group. For each outcome, summary estimates are provided regarding effect size, 95% confidence limits and number of experiments alongside chi squared value (χ^2), *represents stratifications which accounted for a significant proportion of the observed heterogeneity.

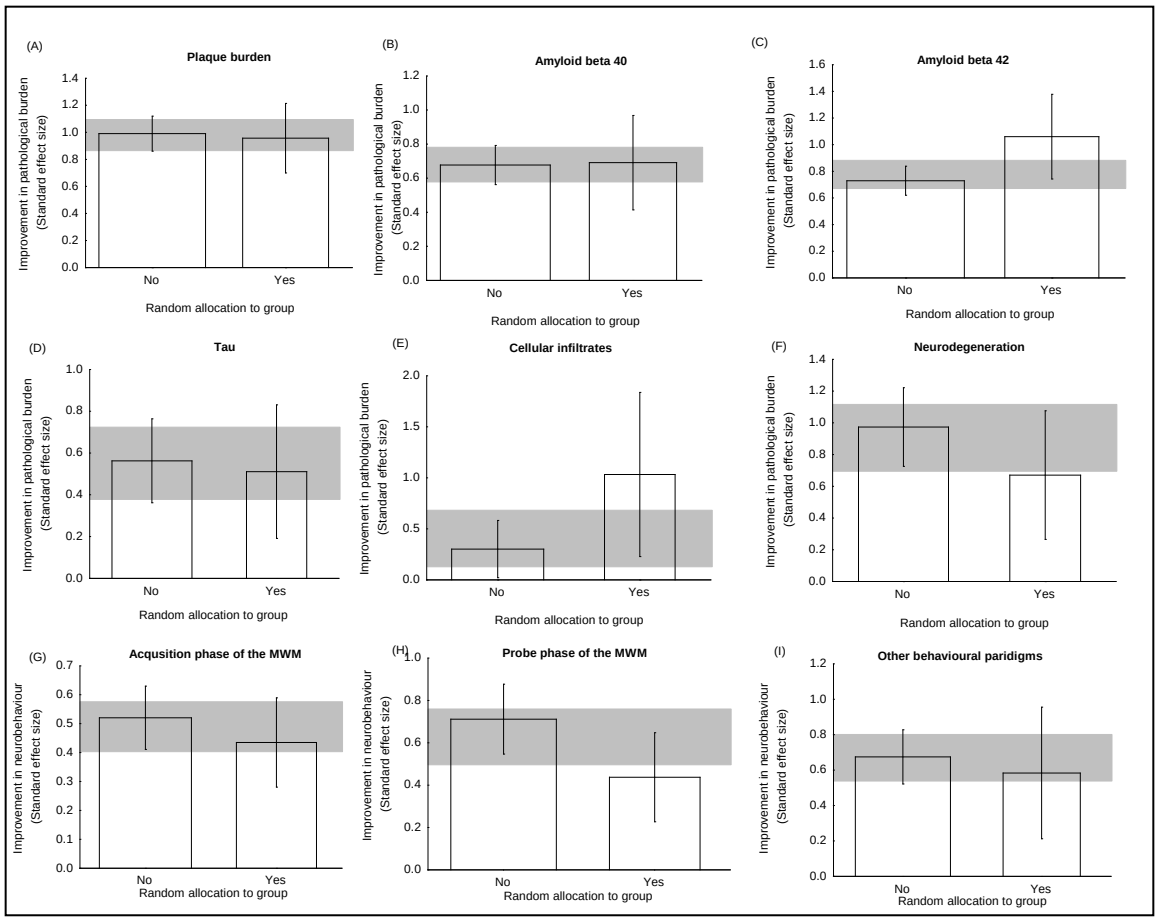


Figure 7.3: I stratified outcomes to identify whether there was an association between effect size and random allocation to group. For each outcome, grey bar represents 95% confidence limit (CI) of global estimate, error bars represent 95% CI of summary estimates and bar width represents the log of the number of animals.

7.1.4 Statement regarding a conflict of interest

I performed a stratified analysis in order to assess the impact of a statement regarding a conflict of interest on overall pathological and behaviour, and for individual outcomes (see Table 7.4 for summary and Figure 7.4 for overview of individual outcomes). For pathological outcomes, I observed that stratifying data according to a statement regarding a conflict of interest accounted for a significant proportion of the observed heterogeneity (χ^2=70.4, p<0.01, 725 observations, Table 7.4). Similarly, stratifying neurobehavioral summary data accounted for a significant proportion of the observed heterogeneity where higher estimates of efficacy were found with a presence of the study quality item (0.75 SD [0.59 to 0.90] vs. 0.58 SD [0.49 to 0.66], χ^2=8.15).

For individual pathological outcomes stratifying both plaque burden and amyloid beta 40 outcomes by a conflict of interest explained a significant proportion of heterogeneity where estimates were higher when present opposed not when not (χ^2 =76.8 [Figure 7.4a], and χ^2= 10.1 p<0.01 [Figure 7.4b], p<0.01 respectively) . Although stratifying amyloid beta 42 data proved significant in terms of heterogeneity, I did not identify differences in estimates (χ^2= 6.81).I did not identify any individual behavioural outcome measures where stratifying data by a conflict of interest could account for a significant proportion of the observed heterogeneity.

Outcome measure	Statement regarding conflict of interest		Combined	Critical χ^2 =6.63 df=1
	Yes	No		
Plaque burden* (antibody stained)	1.5 SD (1.23 to 1.76) **72**	0.84 SD (0.72 to 0.97) **306**	0.98 SD (0.87 to 1.1) **378**	χ^2 = 76.8 **Sig.**
Amyloid beta 40*	0.76 SD (0.54 to 0.99) **57**	0.67 SD (0.55 to 0.78) **331**	0.68 SD (0.57 to 0.79) **388**	χ^2 = 10.1 **Sig.**
Amyloid beta 42	0.8 SD (0.58 to 1.01) **67**	0.77 SD (0.66 to 0.89) **322**	0.78 SD (0.67 to 0.88) **389**	χ^2 = 6.81 **Sig**
NFT	0.35 SD (0.03 to 0.66) **5**	0.59 SD (0.4 to 0.78) **79**	0.55 SD (0.38 to 0.72) **84**	χ^2 = 0.07 **Non sig**
Cell infiltrates	0.69 SD (0.08 to 1.3) 21	0.31 SD (-0.01 to 0.63) **68**	0.4 SD (0.13 to 0.68) **89**	χ^2 = 0.01 **Non sig**
Neurodegeneration	0.97 SD (0.55 to 1.39) **14**	0.88 SD (0.63 to 1.13) **50**	0.91 SD (0.69 to 1.12) **64**	χ^2 = 0.09 **Non sig**
Total pathology*	0.93 SD (0.77 to 1.09) **118**	0.75 SD (0.67 to 0.83) **607**	0.78 SD (0.71 to 0.85) **725**	χ^2 = 70.4 **Sig**
Acquisition phase of MWM	0.52 SD (0.33 to 0.72) 27	0.49 SD (0.39 to 0.60) 103	0.49 SD (0.41 to 0.58) 130	χ^2 = 0.16 **Non sig**
Probe phase of MWM*	0.82 SD (0.54 to 1.1) **16**	0.60 SD (0.45 to 0.74) **97**	0.63 SD (0.5 to 0.76) **113**	χ^2 = 4.99 **Non sig**
Other neurobehavioural studies	0.89 SD (0.61 to 1.16) 33	0.67 SD (0.53 to 0.81) 90	0.72 SD (0.59 to 0.84) 123	χ^2 = 5.13 **Non sig**
Neurobehaviour*	0.75 SD (0.59 to 0.90) 62	0.58 SD (0.49 to 0.66) 197	0.61 SD (0.54 to 0.69) 259	χ^2 = 8.15 **Sig**

Table 7.4: I stratified outcomes to identify whether there was an association between effect size and a statement regarding conflicts of interest. For each outcome, summary estimates are provided regarding effect size, 95% confidence limits and number of experiments alongside chi squared value (χ^2), *represents stratifications which accounted for a significant proportion of the observed heterogeneity.

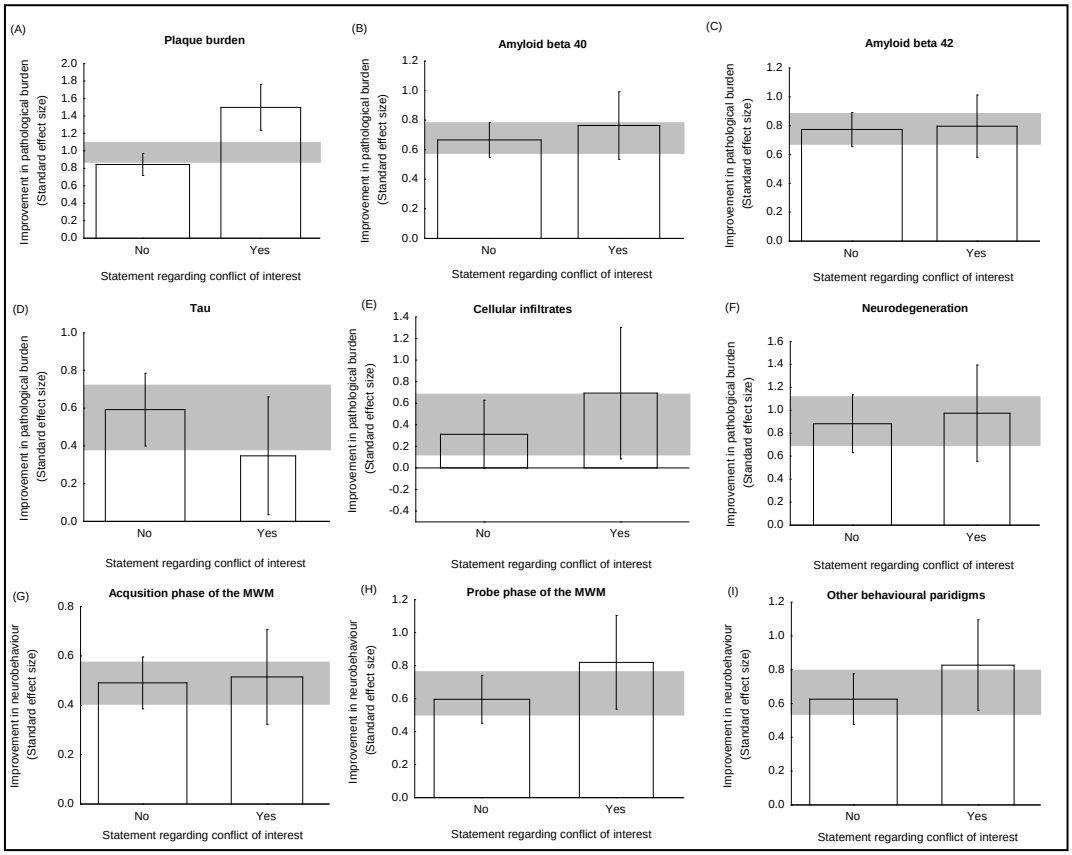


Figure 7.4: I stratified outcomes to identify whether there was an association between effect size and statement regarding a conflict of interest. For each outcome, grey bar represents 95% confidence limit (CI) of global estimate, error bars represent 95% CI of summary estimates and bar width represents the log of the number of animals.

7.1.5 Compliance with animal welfare legislation

I performed a stratified analysis in order to assess the impact of a compliance with animal welfare legislation on overall pathological and behaviour, and for individual outcomes (see Table 7.5 for summary and Figure 7.5 for overview of individual outcomes). For pathological outcomes overall, I observed that stratifying data according to a statement regarding compliance with animal welfare legislation did not account for a significant proportion of the observed heterogeneity. Similarly, neurobehavioral experiments overall did not account for a significant proportion of the observed heterogeneity.

When observing individual pathological outcomes, I identified that amyloid beta 40 (Table 7.5b) and amyloid beta 42 (Table 7.5c) had lower estimates of efficacy with the presence of the study quality feature ($\chi^2 = 7.58$ and $\chi^2 = 18.8$, $p<0.01$ respectively). Conversely, I observed that for outcomes regarding cell infiltrates and neurodegeneration higher estimates of efficacy were present where studies reported a compliance with animal welfare legislation feature ($\chi^2 = 57.3$ and $\chi^2 = 10.9$, $p<0.01$ respectively). I did not identify any an associations between neurobehavioural estimates of efficacy and whether or not publications stated a compliance with animal welfare legislation.

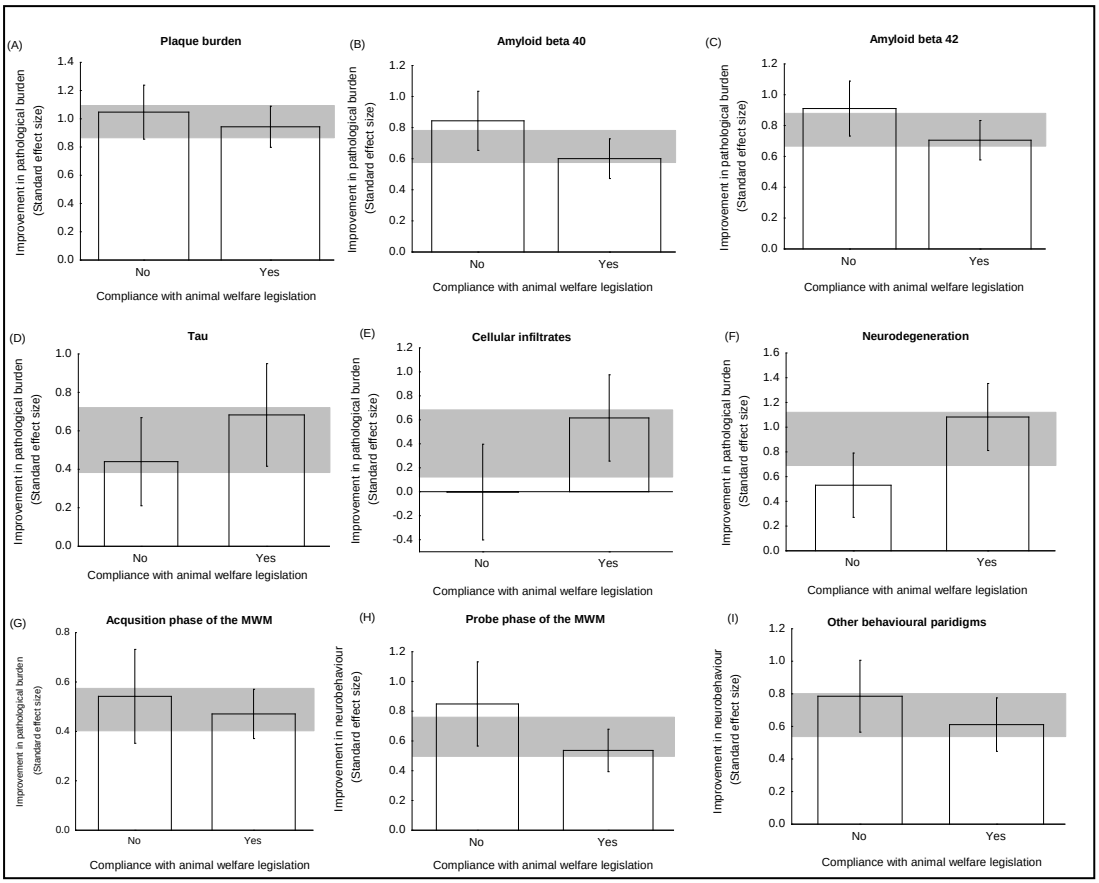


Figure 7.5: I stratified outcomes to identify whether there was an association between effect size and compliance with animal welfare legislation. For each outcome, grey bar represents 95% confidence limit (CI) of global estimate, error bars represent 95% CI of summary estimates and bar width represents the log of the number of animals.

Outcome measure	Compliance with animal welfare legislation		Combined	Critical χ^2 =6.63 df=1
	Yes	No		
Plaque burden (antibody stained)	0.94 SD (0.8 to 1.09) **233**	1.05 SD (0.86 to 1.24) **145**	0.98 SD (0.87 to 1.1) **378**	χ^2 = 0.96 **Non Sig.**
Amyloid beta 40*	0.6 SD (0.47 to 0.73) **263**	0.84 SD (0.65 to 1.03) **125**	0.68 SD (0.57 to 0.79) **388**	χ^2 = 7.58 **Sig**
Amyloid beta 42*	0.71 SD (0.58 to 0.83) **255**	0.91 SD (0.73 to 1.09) **134**	0.78 SD (0.67 to 0.88) **389**	χ^2 = 18.8 **Sig**
NFT	0.68 SD (0.42 to 0.95) **49**	0.44 SD (0.21 to 0.67) **35**	0.55 SD (0.38 to 0.72) **84**	χ^2= 2.1 **Non Sig.**
Cell infiltrates*	0.62 SD (0.26 to 0.98) **57**	0.00 SD (-0.4 to 0.4) **32**	0.4 SD (0.13 to 0.68) **89**	χ^2 = 57.3 **Sig**
Neurodegeneration	1.08 SD (0.81 to 1.35) **44**	0.53 SD (0.27 to 0.79) **20**	0.91 SD (0.69 to 1.12) **64**	χ^2 = 10.9 **Sig**
Pathology	0.77 SD (0.68 to 0.85) **472**	0.81 SD (0.7 to 0.93) **253**	0.78 SD (0.71 to 0.85) **725**	χ^2 = 1.86 **Non Sig.**
Acquisition phase of MWM	0.47 SD (0.38 to 0.57) **91**	0.54 SD (0.35 to 0.73) **39**	0.49 SD (0.41 to 0.58) 130	χ^2 = 0.28 **Non Sig.**
Probe phase of MWM*	0.54 SD (0.39 to 0.68) **77**	0.85 SD (0.57 to 1.13) **36**	0.63 SD (0.5 to 0.76) **113**	χ^2 = 3.03 **Non Sig.**
Other neurobehavioural studies	0.68 SD (0.53 to 0.84) **79**	0.78 SD (0.56 to 1) **44**	0.72 SD (0.59 to 0.84) **123**	χ^2= 0.07 **Non Sig.**
Neurobehaviour	0.56 SD (0.48 to 0.65) **166**	0.71 SD (0.57 to 0.86) **93**	0.61 SD (0.54 to 0.69) **259**	χ^2 = 2.10 **Non Sig.**

Table 7.5: I stratified outcomes to identify whether there was an association between effect size and compliance with animal welfare legislation. For each outcome, summary estimates are provided regarding effect size, 95% confidence limits and number of experiments alongside chi squared value (χ^2), *represents stratifications which accounted for a significant proportion of the observed heterogeneity.

7.1.6 Sample size calculation

No publications presented a sample size calculation so it was not possible to quantify the impact of this study quality item.

7.1.7 Peer review publications

For peer reviewed publications it was not possible to quantify impact as no non reviewed literature (i.e. abstracts) contained data possible to include in the meta-analysis.

7.2 Presence of a wild type group in neurobehavioral outcomes

For neurobehavioral paradigms such as the MWM there is no single ceiling effect expected in performance. Therefore most (but not all) publications reported data from wild type mice to illustrate the maximum behavioural improvement expected within a given paradigm. To further our understanding of whether the presence of a wild type group might impact on observed effect size I stratified data according to whether or not there was a wild type group present in a post hoc analysis.

Our analyses are summarised in Table 7.6. I identified that overall, higher estimates of efficacy were associated with the absence of a wild type group however the only statistically significant difference was for the NORT where estimates were higher where there was a wild type group present. For four out of the six outcomes assessed I identified smaller estimates of efficacy where a wild type group was present, this did not account for a significant proportion of the observed heterogeneity.

Outcome measure	Wild type animals present		Combined	χ 2
	Yes	No		
Acquisition phase of MWM	0.45 (0.35 to 0.55) **94**	0.63 (0.45 to 0.8) **36**	0.49 (0.4 to 0.58) **130**	χ^2 = 3.1 **Non sig**
Probe phase of MWM	0.57 (0.42 to 0.72) **85**	0.81 (0.54 to 1.08) **28**	0.63 (0.5 to 0.76) **113**	χ^2 = 3.04 **Non sig**
Fear conditioning	0.67 (0.25 to 1.1) **35**	0.71 (0.49 to 0.93) **10**	0.7 (0.51 to 0.89) **45**	χ^2 = 0.001 **Non sig**
Radial arm water maze	0.9 (0.65 to 1.15) **37**	0.41 (-0.75 to 1.56) **4**	0.86 (0.61 to 1.1) **41**	χ^2 = 4.15 **Non sig**
Novel object recognition test	1.23 (0.72 to 1.73) **14**	0.62 (0.27 to 0.97) **11**	0.95 (0.63 to 1.27) **25**	χ^2 = 8.38 **Sig**
Y-maze/T-maze	0.45 (0.19 to 0.72) **24**	0.47 (-0.37 to 1.31) **4**	0.46 (0.21 to 0.71) **28**	χ^2 = 0.003 **Non sig**
Total	0.59 (0.5 to 0.67) **194**	0.7 (0.54 to 0.86) **64**	0.61 (0.54 to 0.69) **259**	χ^2 = 1.64 **Non sig**

Table 7.6: I stratified neurobehavioural outcomes to identify whether there was an association between effect size and the presence of a wild type group. For each outcome, summary estimates are provided regarding: effect size, 95% confidence limits, number of experiments alongside chi squared value (χ^2), *represents stratifications which accounted for a significant proportion of the observed heterogeneity.

7.3 Publication bias

I assessed the potential impact of publication bias using Egger regression, Funnel plot asymmetry and trim and fill techniques. I first derived estimates of the impact on pathology and neurobehavioural outcomes overall. I then repeated the analyses on subsets of these datasets using: outcome measures, transgenic model groups and brain regions (where relevant). These analyses were performed to address concerns that a presence publication bias could reflect systematic difference in experimental methodology similar to small study effects.

Investigating individual outcome measures (and brain regions) is crucial to ensure the integrity of these initial findings. For example, it could be that those techniques used to derive estimates of efficacy for plaque burden provide large and precise estimates of effect size. If the converse were true for amyloid beta 40 (small imprecise measures of effect size) then this would give the impression of publication bias. In truth, such differences described are a reflection of those methodologies used not missing studies.

I assessed pathological outcomes overall using Egger regression which indicated a presence of publication bias (Figure 7.6a).Funnel plot asymmetry also suggested a presence of publication bias with a number of missing negative and imprecise effect sizes (Figure 7.6b). A further indication of publication bias was found using trim and fill where a suggested baseline efficacy of 0.749 SD (95% CI 0.702 to 0.796, 2517

experiments) was reduced to 0.419 SD (0.367 to 0.470) after the inclusion of 783 missing studies (Figure 7.6c). For neurobehavioral outcomes overall I found a presence of publication bias with both Egger regression (Figure 7.6d) and publication bias (Figure 7.6e) Trim and fill suggested a baseline efficacy of 0.601 SD (95% CI 0.538 to 0.664, 561 experiments) which was reduced to 0.405 SD (0.334 to 0.476) after the inclusion of 96 missing studies (Figure 7.6f).

Outcome measure	Egger regression	Funnel Plotting	Trim and fill Global Standardised effect size, 95% Confidence limits and N				
			Unadjusted	Adjusted	Number missing (%)	Absolute change in Global estimate (S.D)	Relative change in Global estimate (%)
Pathological outcomes	Y	Y	0.749 0.702 to 0.796 2517	0.419 0.367 to 0.470 3300	783 (23.7%)	0.330	78.8
Neurobehavioural outcomes	Y	Y	0.601 0.538 to 0.664 561	0.405 0.334 to 0.476 657	96 (14.6%)	0.196	48.4

Table 7.7: Summary table of assessing pathological outcomes for the presence of publication bias through Egger regression, Funnel plot asymmetry and Trim and fill techniques. Where Trim and fill identified publication bias both the unadjusted and adjusted estimates of efficacy are given alongside the percentage of experiments which are hypothesised missing.

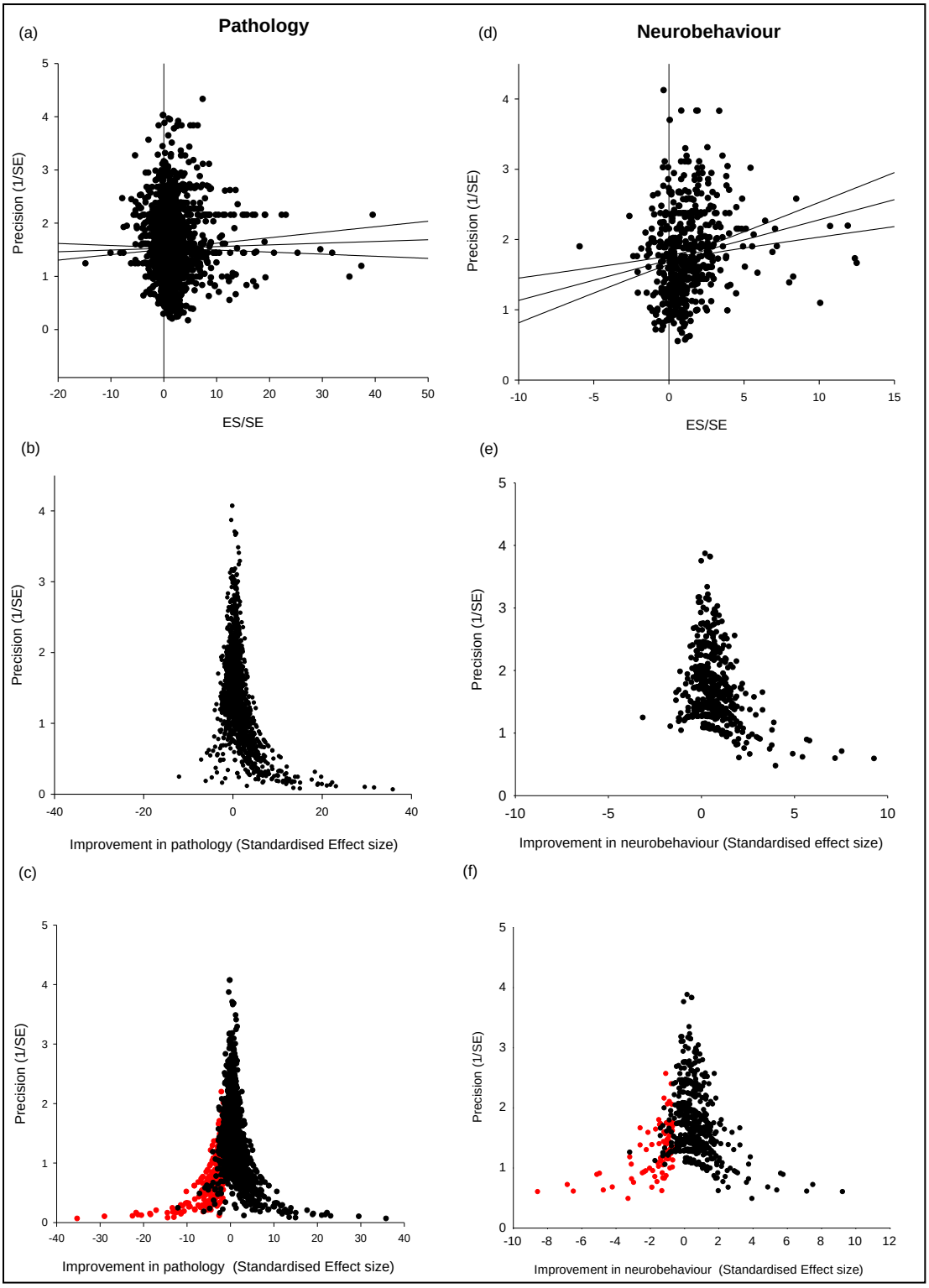


Figure 7.6: Summary data for pathological and neurobehavioral outcomes. Pathological outcomes are assessed by (a) Egger regression, (b) Funnel plot asymmetry and (c) Trim and fill techniques (missing studies shown in red). Likewise neurobehavioural data are assessed through Egger regression, (d) Funnel plot asymmetry and (e) Trim and fill techniques (f).

Individual Pathological outcomes

7.3.1 Plaque burden

For plaque burden data both Egger regression (Figure 7.7a) and Funnel plot asymmetry suggested a degree of publication bias (Figure 7.7b). Trim and fill analysis of 632 outcomes suggested a baseline efficacy of 0.999 SD (95 CI 0.905 to 1.093) revised to 0.610 (95% CI 0.508 to 0.712) after correction for the inclusion of data from 154 imputed missing studies Figure 7.7c).

7.3.2 Amyloid beta 40

For amyloid beta 40 data, both Egger regression (Figure 7.7d) and Funnel plot asymmetry suggested a presence of publication bias (Figure 7.7e) which was confirmed using trim and fill analysis (Figure 7.7f). 625 outcomes suggested a baseline efficacy of 0.635 SD (0.579 to 0.724) which was revised to 0.321 SD (0.221 to 0.421) after the correction of including data from 124 missing studies.

7.3.3 Amyloid beta 42

For amyloid beta 42 data, Egger regression (Figure 7.8a) and Funnel plotting (figure 7.8b) suggested a presence of publication bias which was confirmed using trim and fill techniques. Data from 632 experiments suggested a baseline efficacy of 0.706 SD (0.616 to 0.796) which was reduced to 0.351 SD (0.250 to 0.452) after accounting for the estimated 136 missing studies (Figure 7.8c).

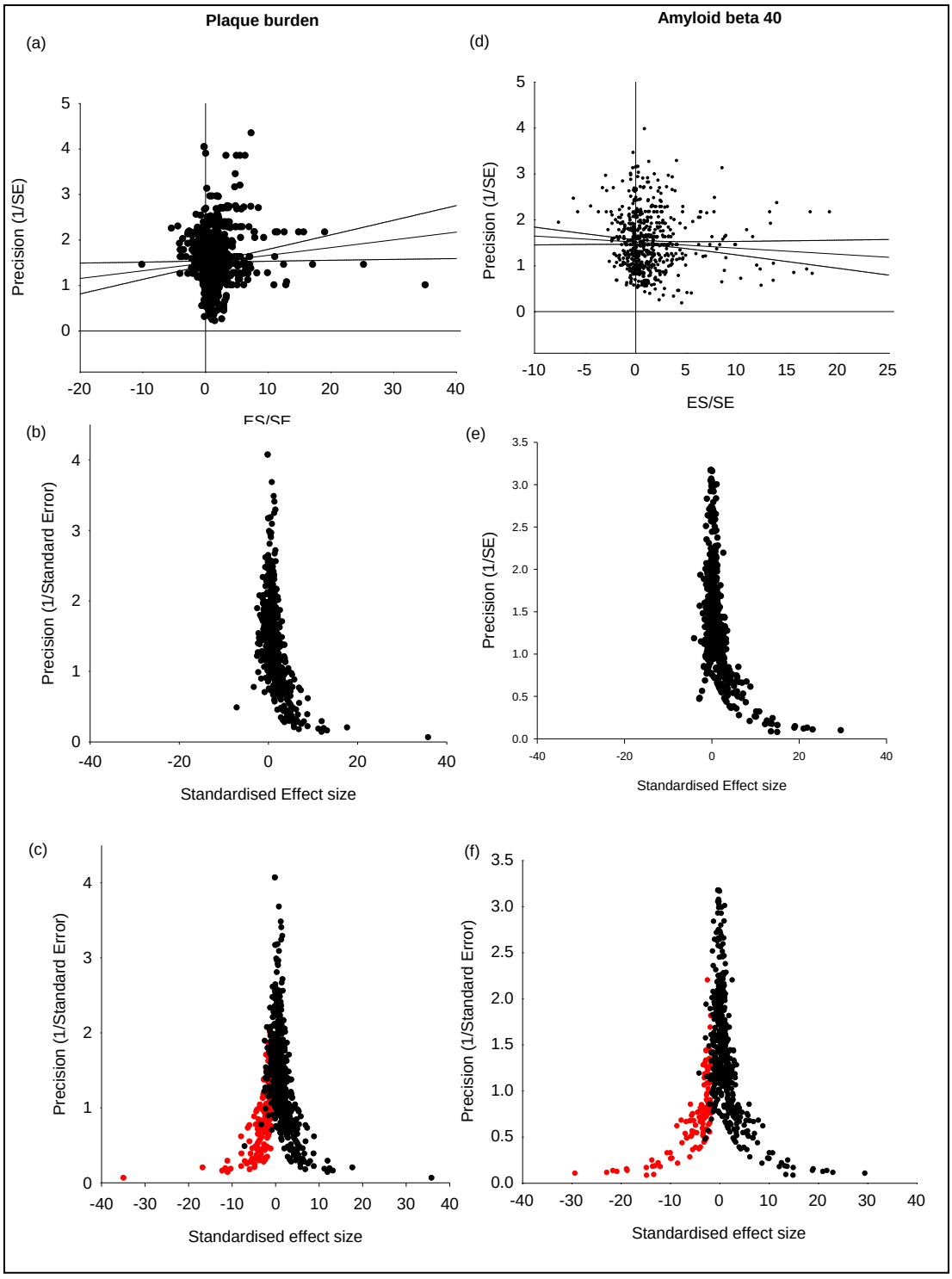


Figure 7.7: Publication bias analyses for plaque burden (a-c) and amyloid beta 40 (d-f). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

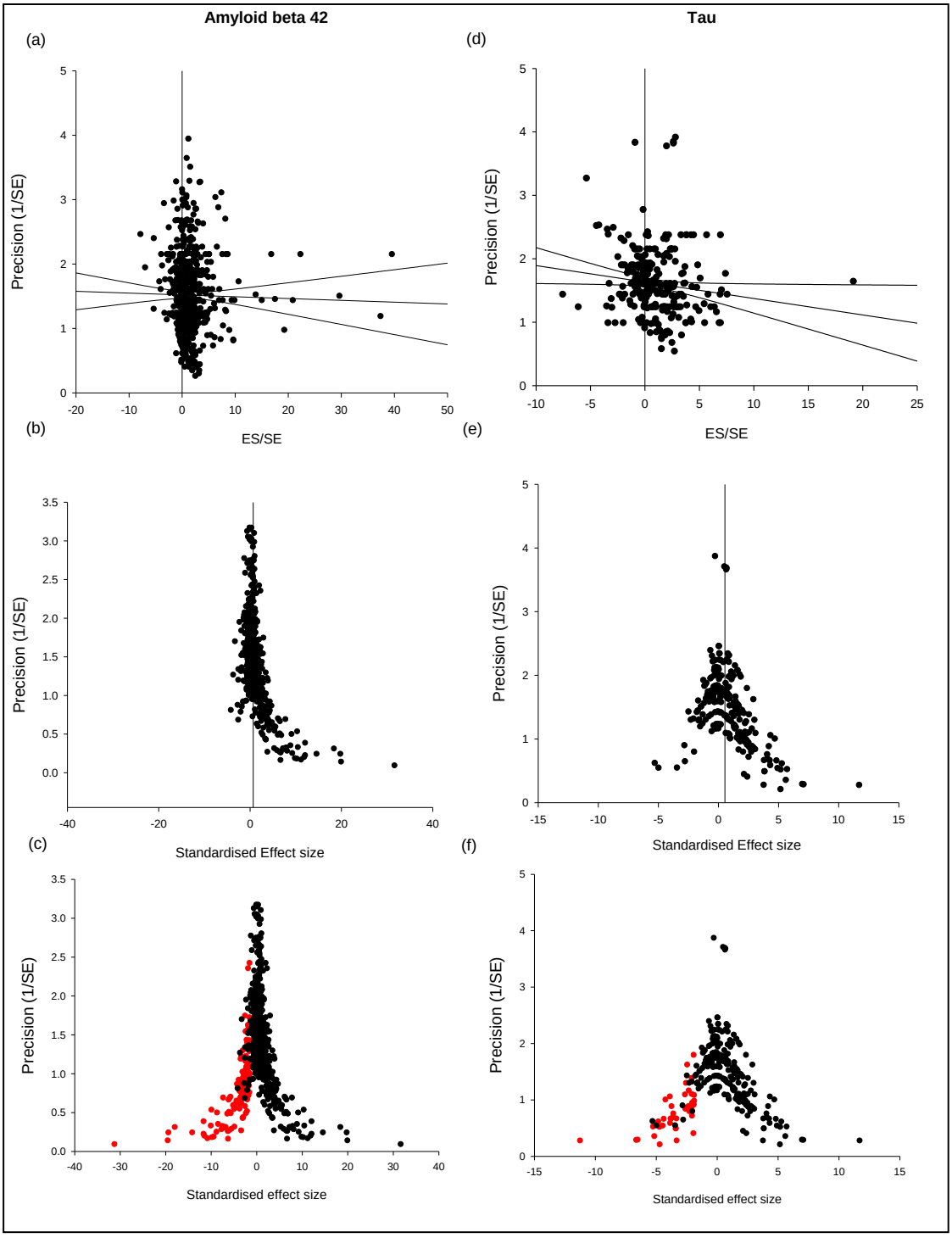


Figure 7.8: Publication bias analyses for amyloid beta 42 (a-c) and tau (d-f). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

7.3.4 Tau

Similar to findings in other outcomes, Egger regression (Figure 7.8d), Funnel plotting (Figure 7.6e) of changes in tau pathology suggested an absence of negative or neutral studies. Further evidence of publication bias was found using trim and fill techniques where baseline efficacy of 0.533 SD (95% 0.400 to 0.666) from 273 experiments was reduced to 0.285 SD (0.141 to 0.430) after the inclusion of 43 missing studies (Figure 7.8f).

7.3.5 Cellular Infiltrates

For outcomes regarding cellular infiltrates Egger regression suggested a presence of publication bias (Figure 7.9a) but this was not replicated in the Funnel plot asymmetry (Figure 7.9b). Assessing such 222 experiments using trim and fill techniques did not alter the overall estimate of efficacy and thus the estimate of efficacy; 0.561 SD (0.367 to 0.755) remained unchanged (Figure 7.9e).

7.3.6 Neurodegeneration

For neurodegeneration outcomes a presence of publication bias was visible in both Egger regression (Figure 7.9d) and Funnel plot asymmetry (Figure 7.9e). From 133 studies, the baseline efficacy was estimated to be 0.962 SD (0.784 to 1.140) which after trim and fill was revised to 0.764 SD (0.566 to 0.961) after the inclusion of 17 missing studies(Figure 7.9f).

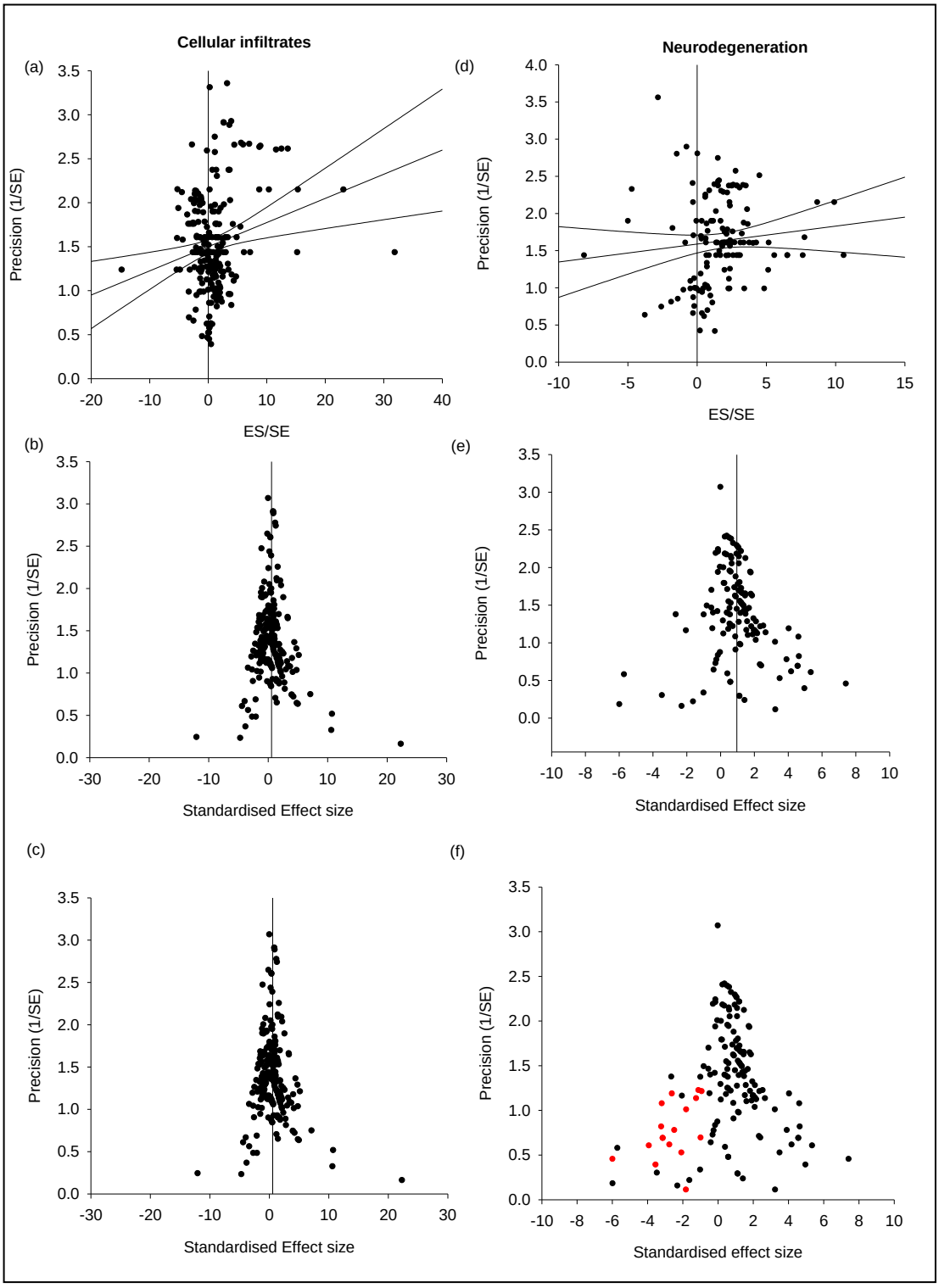


Figure 7.9: Publication bias analyses for cellular infilatrates (a-c) and neurodegeneration (d-f). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

Outcome measure	Egger regression	Funnel Plotting	Trim and fill Global Estimate [Standard Deviations, (95% Confidence limits) and N]			Global estimate	
			Unadjusted	Adjusted	Number missing (%)	Absolute change (S.D)	Relative change (%)
Plaque burden (antibody stained)	Y	Y	0.999 (0.905 to 1.093) 632	0.610 (0.508 to 0.712) 786	154 (19.6)	0.389	63.8%
Amyloid beta 40	Y	Y	0.635 (0.579 to 0.724) 625	0.321 (0.221 to 0.421) 749	124 (16.6)	0.314	97.8%
Amyloid beta 42	Y	Y	0.706 (0.616 to 0.796) 632	0.351 (0.250 to 0.452) 768	136 (17.7)	0.355	101.1%
NFT	Y	Y	0.533 (0.400 to 0.666) 273	0.285 (0.141 to 0.420) 316	43 (13.6)	0.248	87.0%
Cell infiltrates	Y	N	0.561 (0.367 to 0.755) 222	0.561 (0.367 to 0.755) 222	0 (0)	0.00	0%
Neurodegeneration	Y	Y	0.962 (0.784 to 1.140) 133	0.764 (0.566 to 0.961) 150	17 (11.3)	0.198	25.9%
Other pathological outcomes	Y	Y	0.918 (0.792 to 1.045) 331	0.467 (0.328 to 0.605) 413	8 (19.9)	0.451	96.6%

Table 7.8: Summary table of assessing pathological outcomes for the presence of publication bias through Egger regression, Funnel plot asymmetry and Trim and fill techniques. Where Trim and fill identified publication bias both the unadjusted and adjusted estimates of efficacy are given alongside the percentage of experiments which are hypothesised missing.

Overall pathology by brain region

7.3.7 Hippocampus and Cortex estimates of efficacy

From 2517 comparisons used to provide pathological estimates of efficacy, the specific brain region was stated in 1314 (52%). Within these, 92% of estimates were either for the hippocampus (658 comparisons) or cortex (549 comparisons). Therefore I assessed data from both the cortex and hippocampus for a presence of publication bias.

For data from the hippocampus I identified a presence of publication bias with Egger regression (Figure 7.10a) and funnel plotting (Figure 7.10b) where I identified a number of missing negative effect size, low precision estimates. Such findings were confirmed using Trim and Fill where a baseline efficacy of 0.747 SD (95 CI 0.650 to 0.843) which was reduced to 0.370 SD (95 CI 0.263 to 0.477) after the inclusion of 125 missing studies (Figure 7.10c).

For data from the cortex I identified a presence of publication bias with Egger regression and funnel plotting (Figure 7.10d and e). These findings were also confirmed using Trim and Fill where a baseline efficacy of 0.828 SD (95 CI 0.726 to 0.930) which was reduced to 0.446 SD (95 CI 0.333 to 0.558) after the inclusion of 108 missing studies (Figure 7.10f).

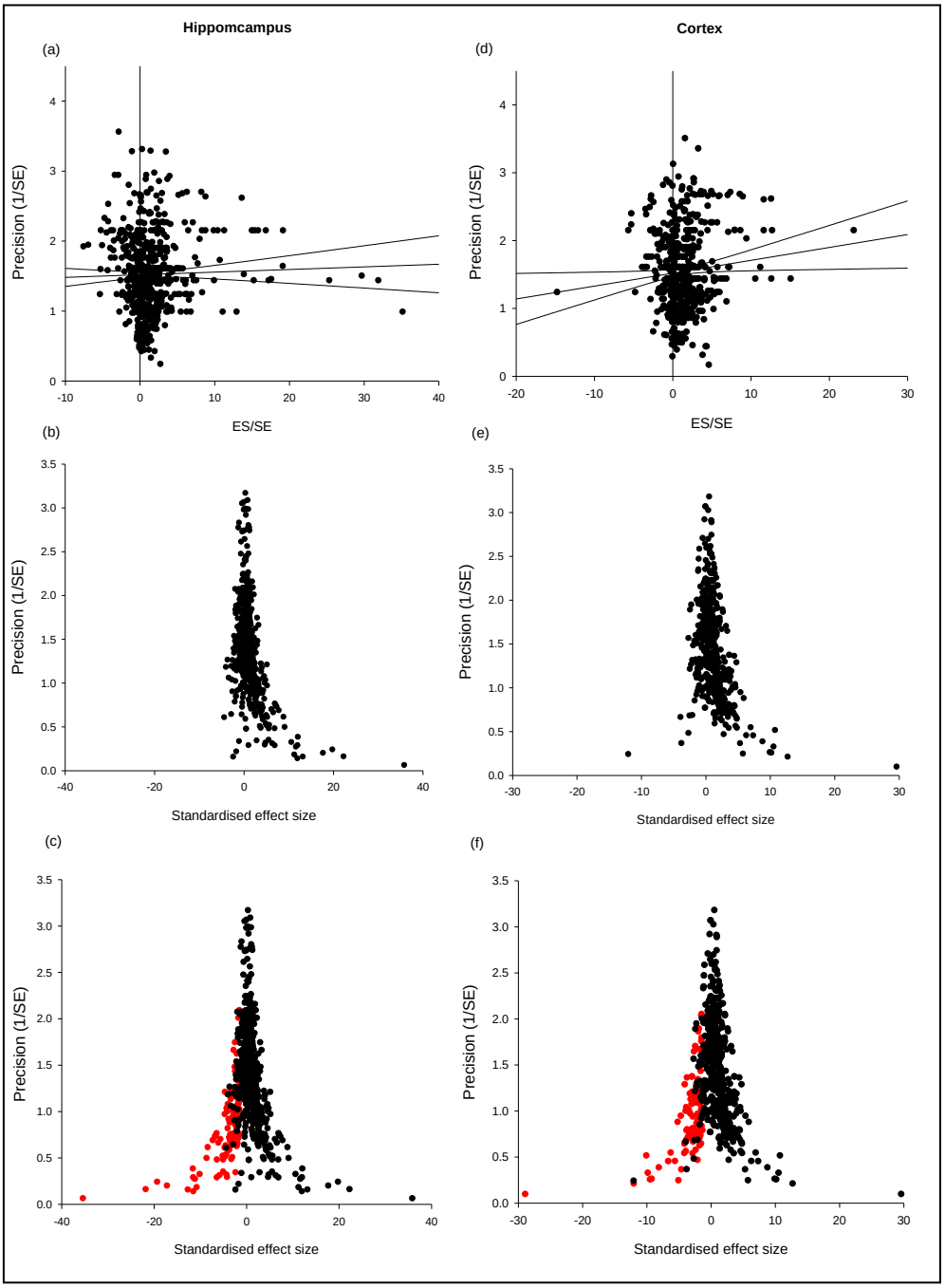


Figure 7.10: Publication bias analyses from the hippocampus (a-c) and cortex (d-f). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

Brain region	Egger regression	Funnel Plotting	Trim and fill Global Estimate [Standard Deviations, (95% Confidence limits) and N]			Global estimate	
			Unadjusted	Adjusted	Number missing	Absolute change (S.D)	Relative change (%)
Hippocampus	Y	Y	0.747 (0.650 to 0.843) 658	0.370 (0.263 to 0.477) 783	125 (16)	0.377	101.9
Cortex	Y	Y	0.828 (0.726to 0.930) 549	0.446 (0.333 to 0.558) 657	108 (16.4)	0.382	85.7

Table 7.9: Summary table of assessing pathological outcomes for the presence of publication bias through Egger regression, Funnel plot asymmetry and Trim and fill techniques. Where Trim and fill identified publication bias both the unadjusted and adjusted estimates of efficacy are given alongside the percentage of experiments which are hypothesised missing.

Individual Neurobehavioral Outcomes

7.3.8 Acquisition phase of Morris water maze

Where I assessed acquisition data I identified an indication of publication bias using both Egger regression (Figure 7.11a) and funnel plot asymmetry (Figure 7.11b). Trim and fill estimates suggested a baseline efficacy 0.489 SD (0.406 to 0.573) which was reduced to 0.353 SD (0.264 to 0.441) after the inclusion of 32 missing studies (Figure 7.11c)

7.3.9 Probe phase of Morris water maze

Similar to acquisition data, both Egger regression and funnel plot asymmetry indicated publication bias for outcomes from the probe phase of the MWM (Figures 7.11d and 7.11e respectively). Trim and fill analysis of 212 outcomes suggested a baseline efficacy of 0.623 SD (95 CI 0.503 to 0.744) which was reduced to 0.400 SD (95 CI 0.262 to 0.539) after the inclusion of 32 missing studies (Figure 7.11f). To ensure the presence of publication bias did not reflect differences in the methods of behavioural assessment I performed a sensitivity analysis where only data for 'time in target quadrant' were used. Trim and fill analysis of 80 outcomes suggested a baseline efficacy of 0.688 SD (95 CI 0.534 to 0.842) which was revised to 0.498 (95 CI 0.324 to 0.672) after correction for the inclusion of data from 15 imputed missing studies (not shown).

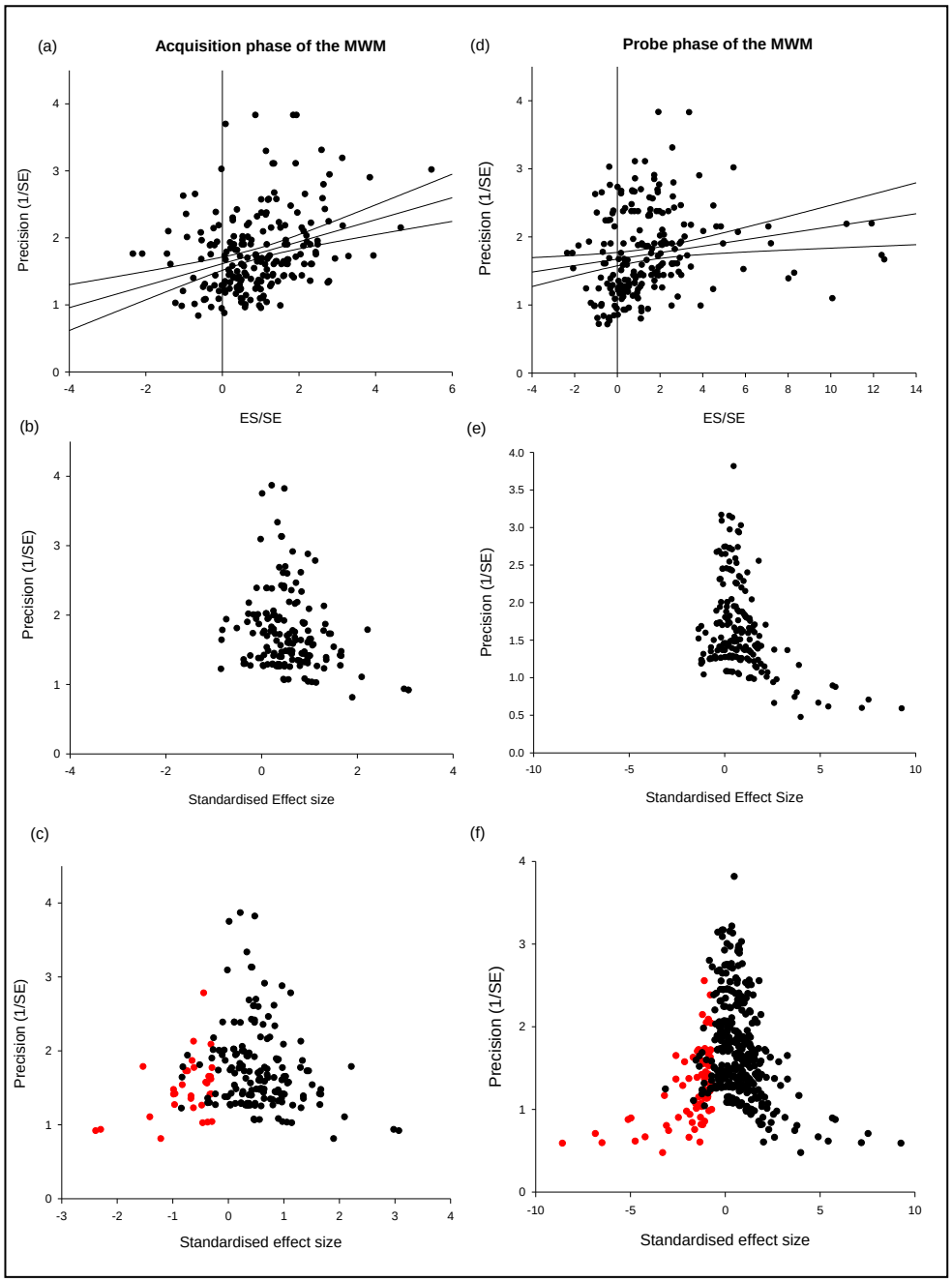


Figure 7.11: Publication bias analyses for the acquisition phase (a-c) and probe phase (d-f) of the Morris water maze (MWM). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

7.3.10 Fear conditioning

For data regarding fear conditioning, Egger regression suggested publication bias, but it was difficult to interpret asymmetry on the funnel plot (Figures 7.12a and 7.12b respectively). Trim and fill analysis of 60 outcomes suggested a baseline efficacy of 0.693 SD (0.495 to 0.890) which was reduced to 0.503 SD (0.297 to 0.709)after the inclusion of 10 missing studies (Figure 7.12c). This translated to a 37.8% reduction in global estimate.

7.3.11 Radial arm water maze

For data from the radial arm water maze Egger regression and Funnel plotting both suggested a degree of publication bias (see Figure 7.12d and 7.12e respectively). Trim and fill analysis of 52 outcome suggested a baseline efficacy of 0.804 SD (0.585 to 1.204) which was reduced to 0.507 SD (0.279 to 0.735) after the inclusion of 16 missing studies (See figure 7.12f).

7.3.12 Novel object recognition task

Both Egger regression and funnel plot asymmetry suggested publication bias was present within the NORT dataset (Figure 7.13a and 7.13b respectively). Trim and fill analysis of 30 outcomes suggested a baseline efficacy of 0.904 SD (0.62 to 1.119) which was reduced to 0.629 SD (0.300 to 0.959) after the inclusion of 6 missing studies (Figure 7.13c).

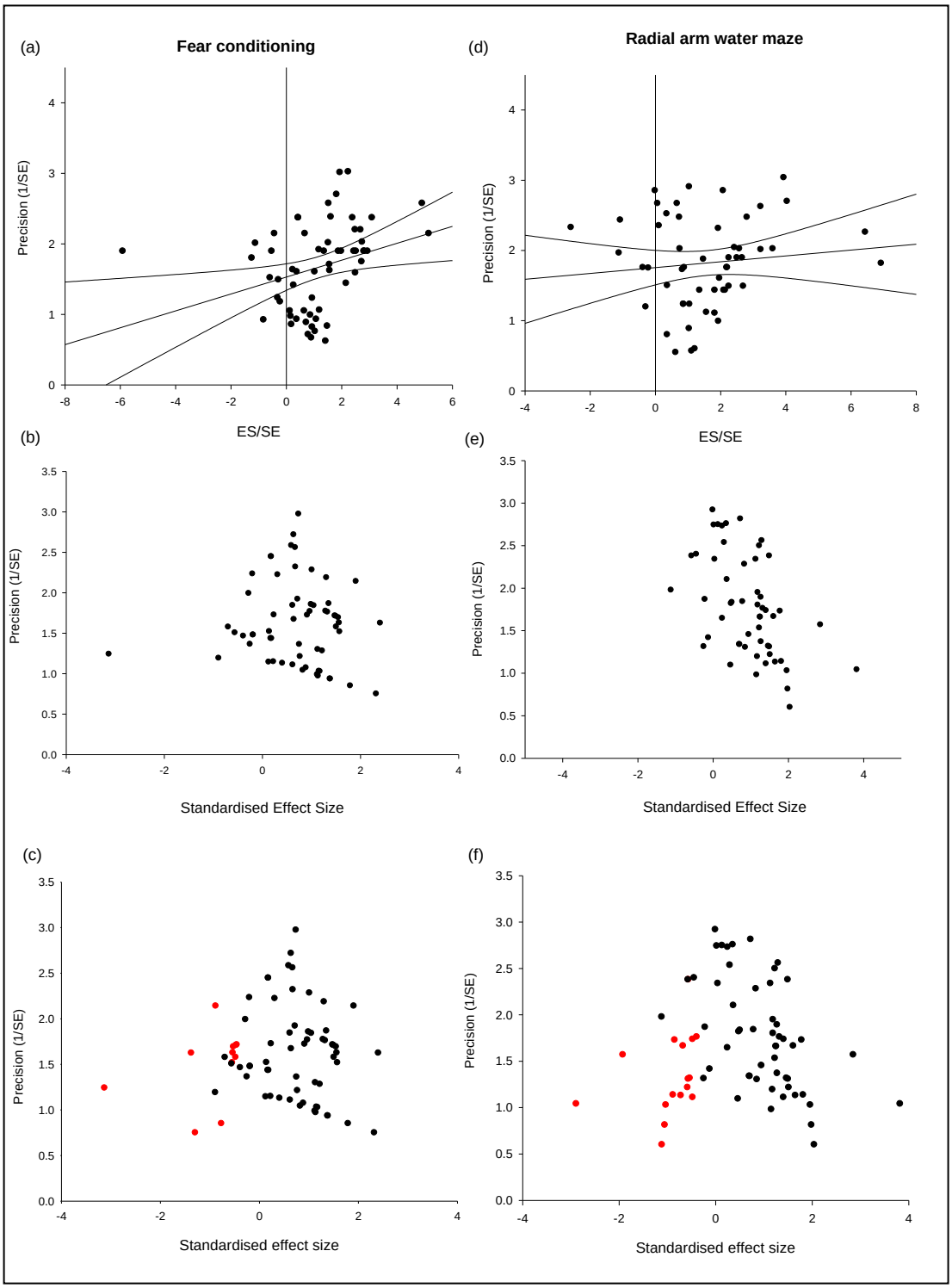


Figure 7.12: Publication bias analyses for fear conditioning (a-c) and the radial arm water maze. Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

7.3.13 T maze & Y maze

Both Egger regression and Funnel plot asymmetry suggested a degree of publication bias for T maze and Y maze data (Figure 7.13d and e). This was subsequently confirmed using Trim and fill analysis: a baseline efficacy of 0.382 SD (0.166 to 0.597) from 42 outcomes was reduced to 0.299 SD (0.068 to 0.530) after the inclusion of 3 missing studies (figure 7.13f).

7.3.14 Other pathological outcomes

To ensure those datasets analysed for publication bias were not unduly influenced by the absence of data previously excluded (e.g. congo red and thioflavins S stained plaques, total amyloid beta and oligomer species) I grouped such data together for another publication bias analysis. Both Egger regression and funnel plot asymmetry suggested a degree of publication bias (See Table 7.9 for summary and Figure 7.14). I identified 328 studies which had had a baseline efficacy of 0.927(0.800 to 1.054) which was reduced to 0.464 (0.324 to 0.603) after the inclusion of 83 missing studies.

7.3.15 Other neurobehavioral outcomes

Equally, to ensure the exclusion of data which did not feature in 10 or more publications did not induce a bias in results I performed a sensitivity analysis on such data hereafter termed “other neurobehavioral outcomes”. This analysis was performed excluding data from the elevated plus maze or open field test (see methods) I found a suggestion of publication bias within both Egger regression and funnel plotting (Figure 7.14, Table 7.6 for summary) and trim and fill analysis of 85 outcomes suggested that there were 14 missing outcomes; reducing efficacy from 0.504 (0.299 to 0.710) to 0.264 (0.025 to 0.503).

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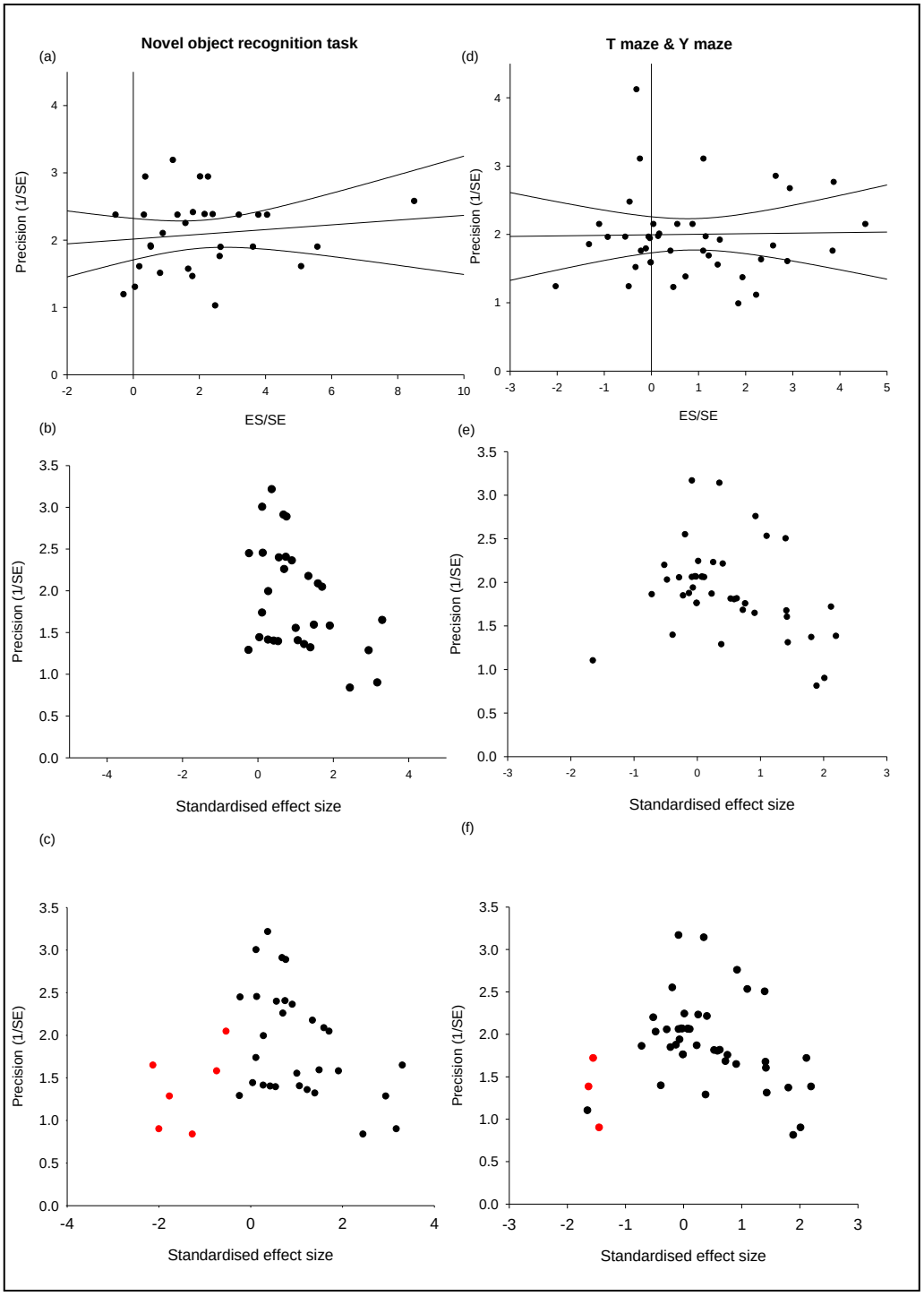

Figure 7.13 Publication bias analyses for novel object recognition task (a-c) and combined data from the T-maze and Y-maze. Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

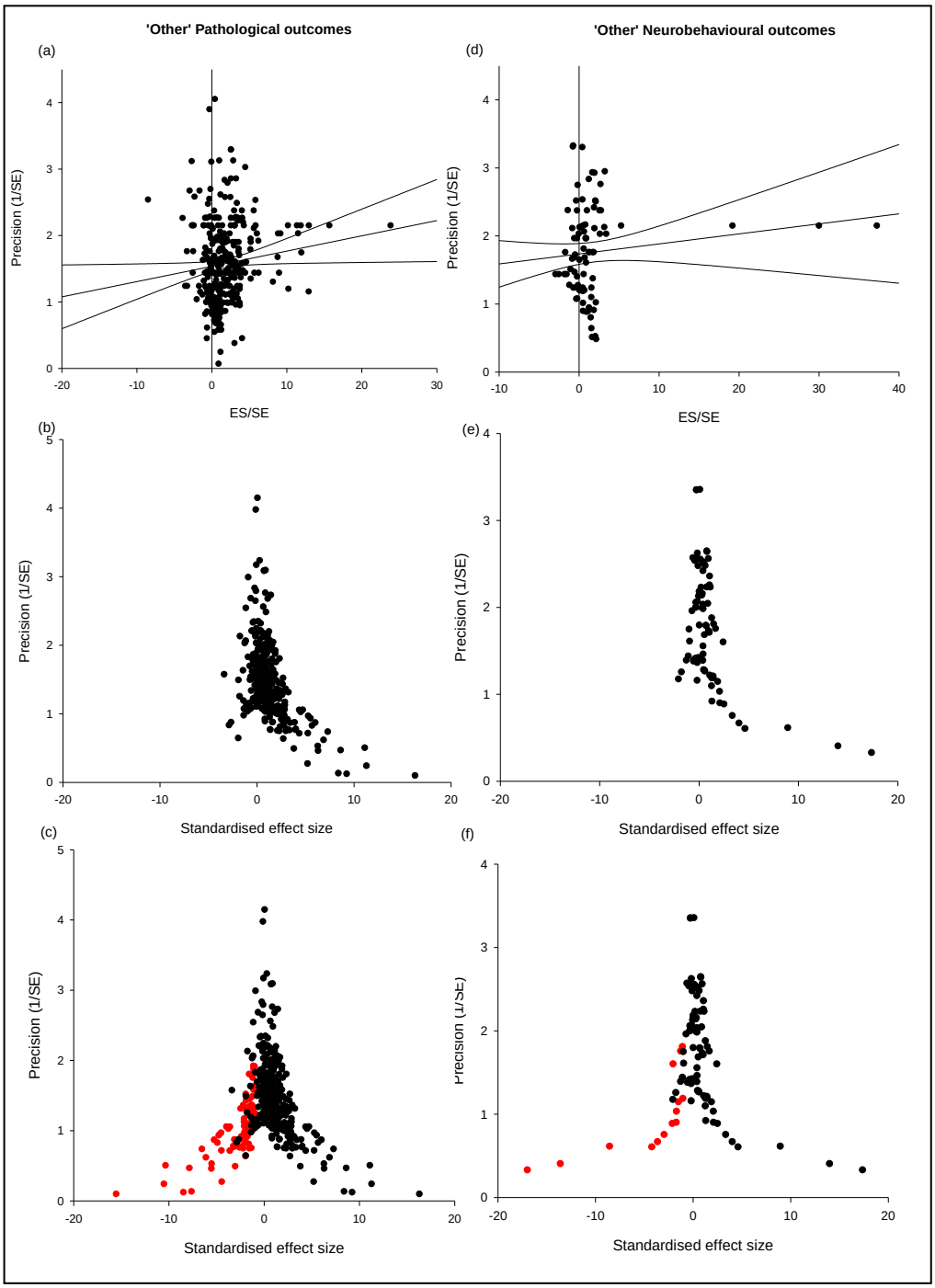

Figure 7.14: Publication bias analyses for pathological (a-c) and behavioural outcomes (d-f) extracted but which were not previously analysed. Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

Outcome measure	Egger regression	Funnel Plotting	Trim and fill Global Estimate [Standard Deviations, (95% Confidence limits) and N]			Global estimate	
			Unadjusted	Adjusted	Number missing (%)	Absolute change (S.D)	Relative change (%)
Acquisition phase of MWM	Y	Y	0.489 (0.406 to 0.573) 164	0.353 (0.264 to 0.441) 196	32 (16.3)	0.136	38.8
Probe phase of MWM	Y	Y	0.623 (0.503 to 0.744) 212	0.400 (0.262 to 0.539) 244	32 (13.0)	0.223	55.8
Fear conditioning	Y	Y	0.693 (0.495 to 0.890) 60	0.503 (0.297 to 0.709) 70	10 (14.3)	0.190	37.8
Radial arm water maze	Y	Y	0.804 (0.585 to 1.024) 53	0.507 (0.279 to 0.735) 69	16 (23.1)	0.297	58.6
T and Y maze	Y	Y	0.382 (0.166 to 0.597 42	0.299 (0.068 to 0.530) 45	3 (6.7)	0.083	27.8
Novel object recognition task	Y	Y	0.904 (0.618 to 1.190) 30	0.629 (0.300 to 0.959) 36	6 (16.7)	0.275	43.7
Other neurobehavioral outcomes	Y	Y	0.497 (0.290 to 0.704) 85	0.254 (0.014 to 0.494) 99	14 (14.1)	0.243	96.6

Table 7.9: Summary table of assessing neurobehavioural outcomes for the presence of publication bias through Egger regression, Funnel plot asymmetry and Trim and fill techniques. Where Trim and fill identified publication bias both the unadjusted and adjusted estimates of efficacy are given alongside the percentage of experiments which are hypothesised missing.

Transgenic model group

7.3.16 Pathology

While publication bias was suggested from the pathological dataset overall I assessed whether this could be explained by differences between transgenic mouse model groups (Table 7.10 and Figures 7.16 to 7.18). I identified that within the APP transgenic mouse model group, both Egger regression and funnel plot asymmetry suggested publication bias. Such suggestions were also confirmed using trim and fill estimates where 1666 comparisons suggested a baseline efficacy of 0.785 (0.727 to 0.842) which was reduced to 0.447 (0.383 to 0.511) after the inclusion of 331 missing studies.

APPS1, 3xTgAD and 'other ' transgenic mice all indicated publication bias through Egger regression (Figure 7.16d, 7.17a, 7.17d and 7.18a respectively) and funnel plot asymmetry (Figure 7.16e, 7.17b, 7.17e and 7.18b respectively). Likewise, trim and fill estimates suggested missing negative of neutral studies for APPS, 3xTgAD and 'other' transgenic mice with the largest relative reduction observed in 3xTgAD mice where a 332 comparisons suggested a baseline efficacy of 0.504 (0.380 to 0.629) which was reduced to 0.261 (0.124 to 0.398) after the inclusion of 47 missing studies

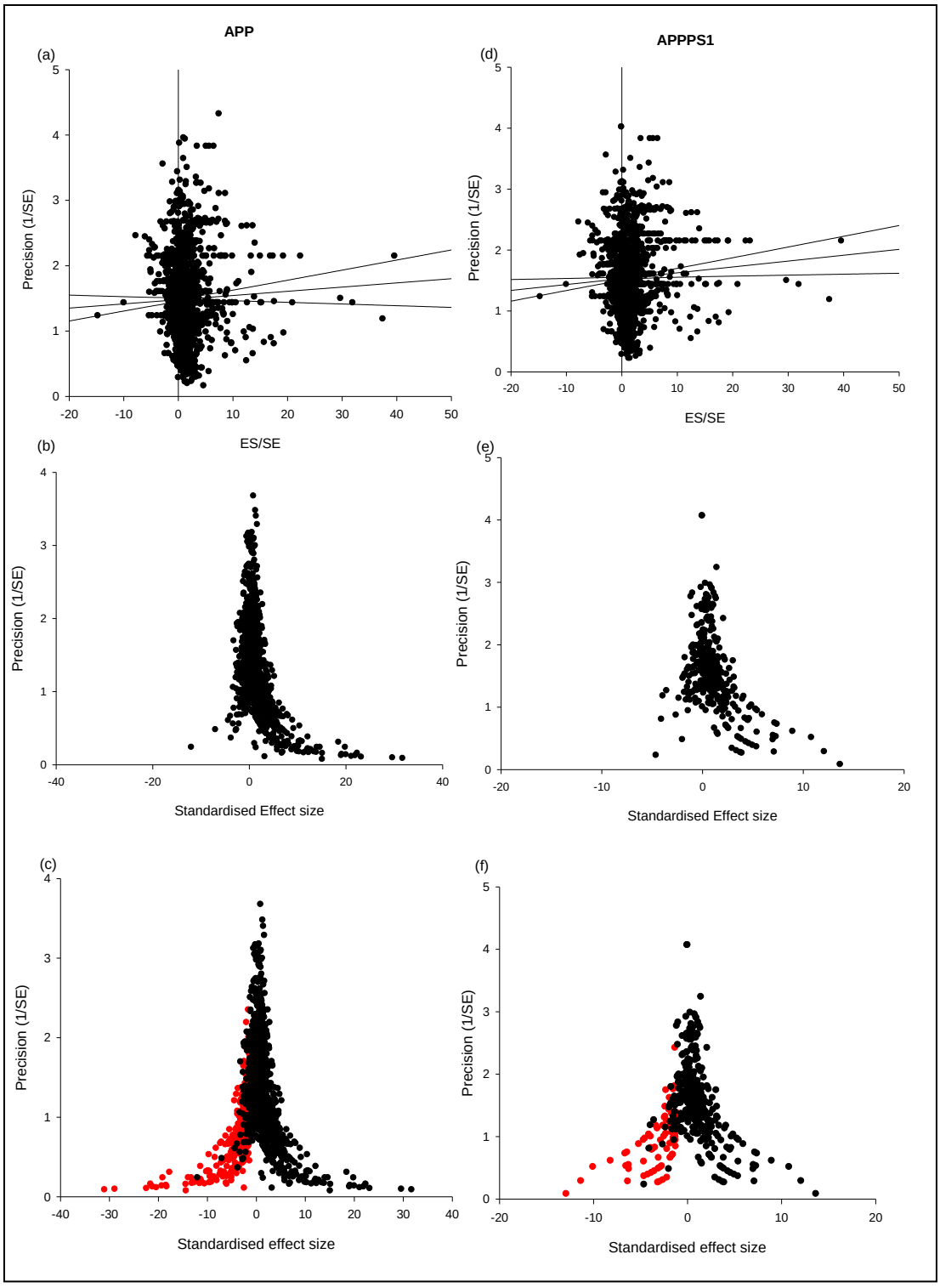

Figure 7.16: Publication bias analyses for the APP transgenic group (a-c) and the APPPS1 transgenic goup (d-f). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

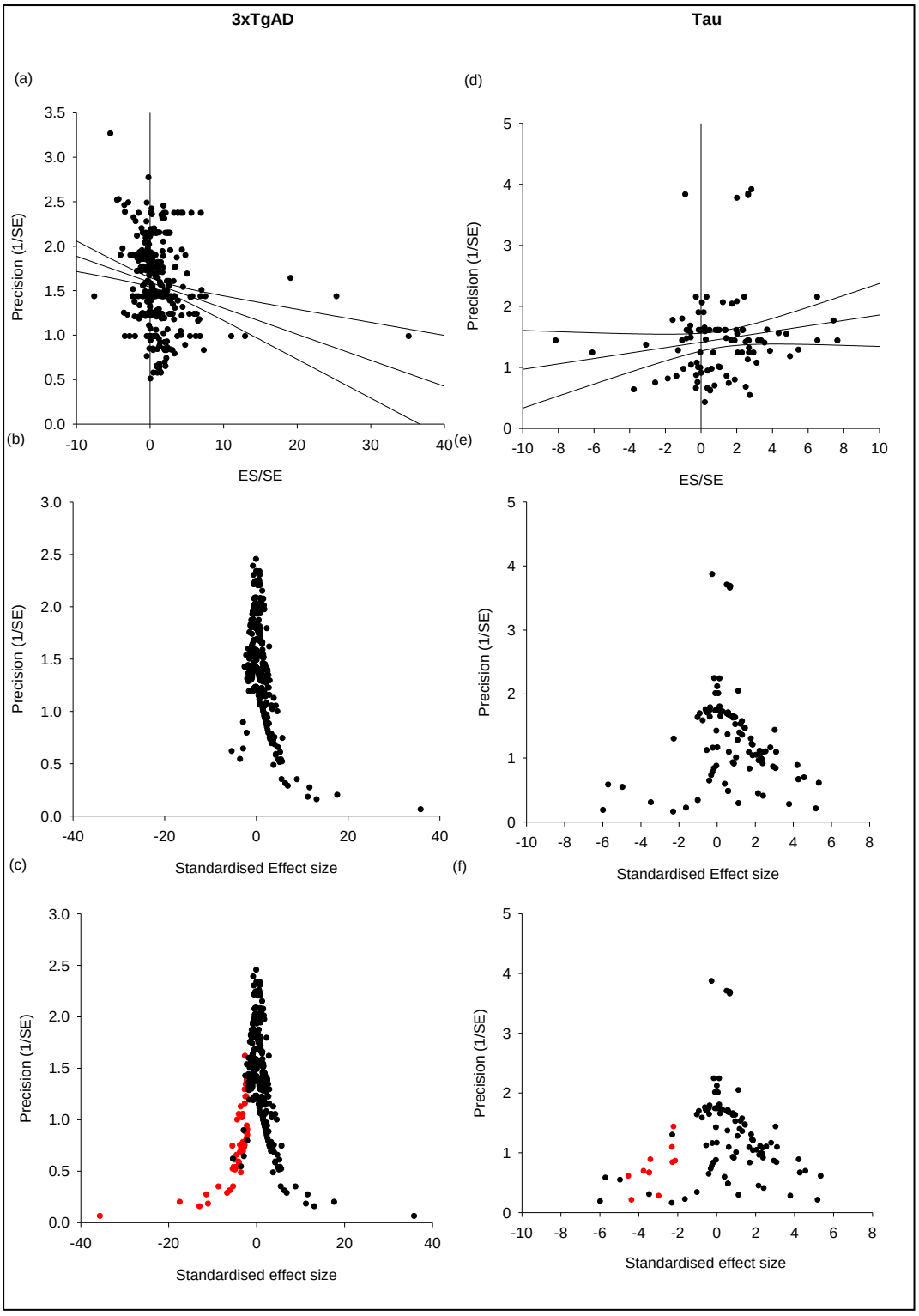

Figure 7.17: Publication bias analyses for the 3xTgAD transgenic group (a-c) and the Tau transgenic goup (d-f). Each outcome was assessed for publication bias using Egger regression (a,c), Funnel plot asymmetry (b,d) and Trim and Fill techniques (c,f). Missing studies from Trim and Fill techniques are shown in red.

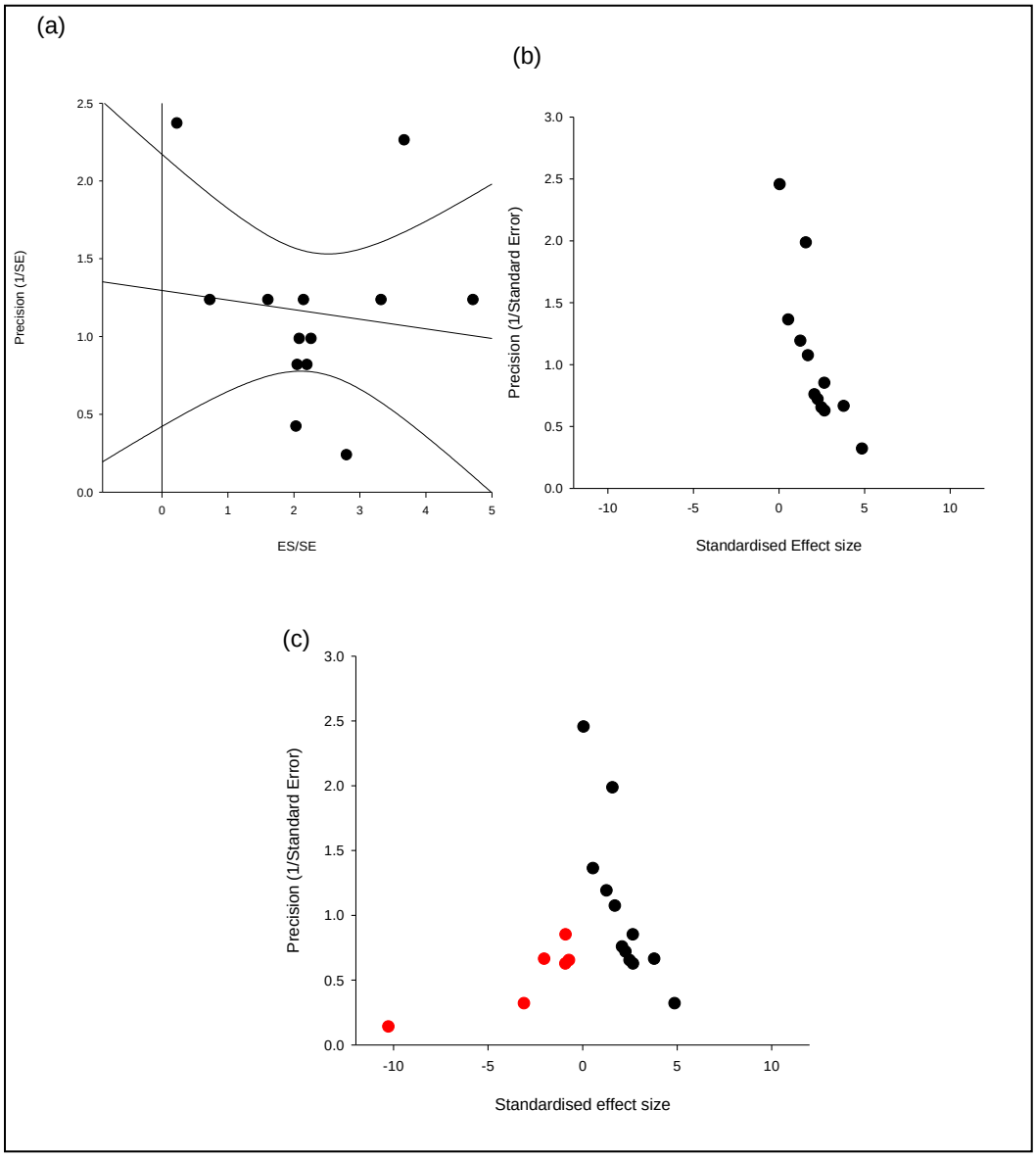

Figure 7.18: Publication bias analyses for the 'other' transgenic group (a-c). Each outcome was assessed for publication bias using Egger regression (a), Funnel plot asymmetry (b) and Trim and Fill techniques (c). Missing studies from Trim and Fill techniques are shown in red.

Transgenic model group	Egger regression	Funnel Plotting	Trim and fill Global Estimate [Standard Deviations, (95% Confidence limits) and N]				
			Unadjusted	Adjusted	Number missing and (%)	Absolute change in Global estimate (S.D)	Relative change in Global estimate (%)
APP	Y	Y	0.785 (0.727 to 0.842) 1666	0.447 (0.383 to 0.511) 1997	331 (16.6)	0.338	75.6
APPPS1	Y	Y	0.802 (0.687 to 0.917) 403	0.418 (0.219 to 0.544) 488	85 (17.4)	0.384	91.9
3xTgAD	Y	Y	0.504 (0.380 to 0.629) 332	0.261 (0.124 to 0.398) 379	47 (12.4)	0.243	93.1
Tau	Y	Y	0.686 (0.468 to 0.905) 101	0.502 (0.264 to 0.739) 112	11 (9.8)	0.184	36.7
PS1			Insufficient data	(2 observations)			
Other	Y	Y	1.599 (0.879 to 2.318) 13	1.104 (0.374 to 1.833 19	6 (31.6)	0.495	44.8

Table 7.10: Summary table of assessing pathological outcomes by individual transgene across Egger regression, Funnel plot asymmetry and Trim and fill techniques. Where Trim and fill identified publication bias both the unadjusted and adjusted estimates of efficacy are given alongside the percentage of experiments which are hypothesised missing.

7.3.17 Neurobehaviour

After identifying publication bias collectively across neurobehavioral outcomes I additionally assessed for publication by transgenic model group in order to assess whether this could account for potential differences (see Table 7.11 and Figures 7.19). Within the APP transgenic mouse model group, both Egger regression and funnel plot asymmetry suggested publication bias. Such suggestions were confirmed using trim and fill where a baseline efficacy of 0.663 SD (0.580 to 0.746) from 346 studies was reduced to 0.471 (0.374 to 0.567) after the inclusion of 52 missing studies.

Similarly, I identified publication bias in both APPPS and 3xTgAD where both funnel plotting and Egger regression suggested publication bias was present (Figure 7.19). For tau, PS and 'other' outcomes it was not possible to assess the impact publication bias using Trim and fill estimates as there were too few studies present for a reliable analysis (5, 7 and 9 comparisons respectively).

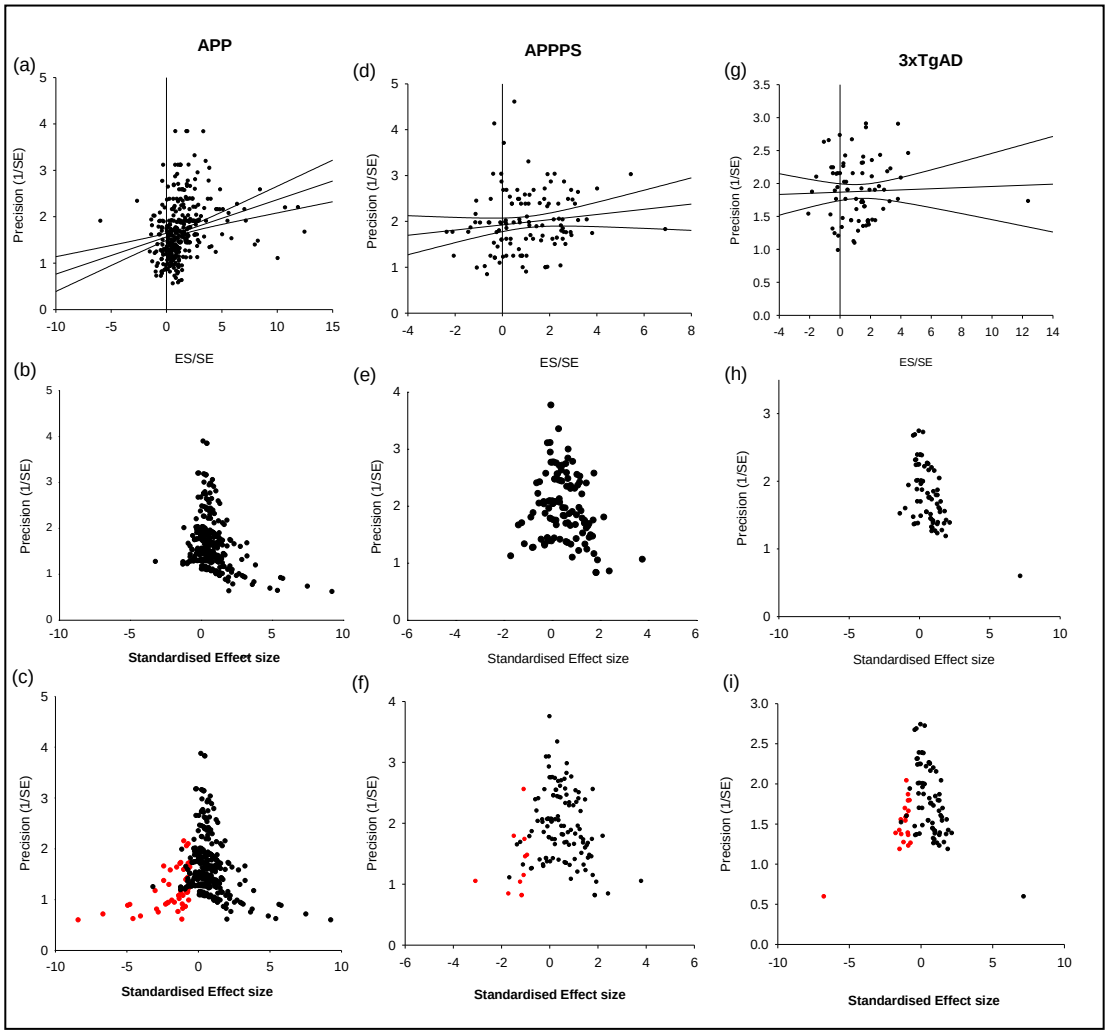

Figure 7.19: Publication bias analyses for the APP transgenic group (a-c) and the APPPS transgenic group (d-f) and 3xTgAD transgenic group (g-i). Each outcome was assessed for publication bias using Egger regression (a,c.g), Funnel plot asymmetry (b,d,g) and Trim and Fill techniques (c,f,i) where missing studies shown in red.

Transgenic model group	Egger regression	Funnel Plotting	Trim and fill Global Estimate [Standard Deviations, (95% Confidence limits) and N]				
			Unadjusted	Adjusted	Number missing And (%)	Absolute change in Global estimate (S.D)	Relative change in Global estimate (%)
APP	Y	Y	0.663 (0.580 to 0.746) 346	0.471 (0.374 to 0.567) 398	52 (13.1)	0.192	40.8
APPPS1	Y	Y	0.489 (0.363 to 0.616) 118	0.395 (0.259 to 0.530) 129	11 (8.53)	0.094	23.8
3xTgAD	Y	Y	0.542 (0.377 to 0.706) 76	0.265 (0.083 to 0.447) 96	20 (20.8)	0.277	104.5
Tau			Insufficient data	(5 observations)			
PS1			Insufficient data	(7 observations)			
Other			Insufficient data	(9 observations)			

Table 7.11: I assessed whether publication bias was present in behavioural outcomes by individual transgene across Egger regression, Funnel plot asymmetry and Trim and fill techniques. Where trim and fill identified publication bias both the unadjusted and adjusted estimates of efficacy are given alongside the percentage of experiments which are hypothesised missing.

7.4. Interpreting study quality and publication bias analyses

7.4.1 Summary of findings

Overall, study quality across transgenic model experiments is relatively low. For individual pathological outcomes the direction of impact in terms of effect size was inconsistent across aggregate study quality and individual study quality items.

For neurobehavioural outcomes, stratifying outcomes according to reported aggregate study quality was also inconclusive. Individual study quality items such as blinding and randomisation were frequently associated with smaller estimates of effect size but these rarely accounted for a significant proportion of the observed heterogeneity. It is likely that some outcomes are more susceptible to the impact of blinding, and it may be that behavioural outcome assessment is more subjective opposed to pathological outcomes. The presence of a wild type group was frequently associated with smaller estimates of effect but this did not prove statistically significant.

I identified publication bias for pathological and neurobehavioural outcomes. Where I performed analyses on specific outcomes, transgenic model groups and brain areas I identified publication bias in all analyses with the exception of trim and fill for cellular infiltrates. Overall estimates suggest 1 in 5 pathological

experiments and 1 in 7 neurobehavioural remain unpublished which causes a relative reduction in efficacy of 78.8% and 48.4% respectively.

7.4.2 Implications of findings

I identified that the reporting of fundamental study quality items was relatively low. While the empirical data did not suggest statistically significant associations between study quality and effect size, randomised and blinded studies were consistently associated with smaller neurobehavioural effect sizes. Thus the impacts of blinding and randomisation, at least from the empirical data appear to be smaller than in animal models of stroke.

The general message from publication bias analyses is clear; there remains a large body of missing negative or neutral studies and these substantially revise our estimates of efficacy. Such reading is concerning because missing data skews our perception of how well interventions perform and is problematic because it encourages; (a) clinical trials to be based on incomplete datasets and (b) needless repletion of animal experiments at the preclinical trial stage.

To improve the situation I think there is an urgent need for the development of a freely accessible online database to summarise experiments conducted in preclinical trials in Alzheimer's disease. In Chapter 8 I discuss efforts made through the work of this thesis to provide an online facility where researchers can report data (past or

present) from any experiment conducted (and in particular those studies with neutral or negative results). We plan to use data collected for this thesis to help design future preclinical and clinical experiments in a similar way.

8: Systematic review in other disease models and development of an online database in transgenic mouse models of Alzheimer's disease

Across this thesis I identified a number of prominent issues regarding the testing of interventions in transgenic mouse models of AD including study quality, study methodology and publication bias. Alongside the main focus of this thesis, there have been a number of significant projects I have been involved with concerning similar themes. For example, issues of study methodology and study quality were highlighted in two published articles, one focused on stem cell therapies and the other on a survey of studies published in the Journal of Cerebral Blood Flow and Metabolism (JCBFM). I have also written a submitted manuscript on the impacts of exercise in preclinical models of stroke which is also a proposed preventative strategy for AD. Finally, during the course of this PhD we have made some potential progress to help address publication bias concerns through providing an online reporting facility for experimental data.

8.1 Stem cell-based therapy for experimental stroke

Across neurological disorders including Alzheimer's disease considerable promise has emerged with the use of stem cells. As part of my studies I worked with colleagues to further our understanding of the potential weaknesses of the use of stem cells in experimental stroke. My specific role was to extract data from publications in order to permit subsequent analyses.

From searching four online databases using a number of key search terms we identified an initial 6059 publications of which 117 met the inclusion criteria. Within these, 70 reported structural and functional outcomes, 11 reported infarct volume and 36 reported neurobehaviour alone. The reported study quality within these publications was 4 out of a possible 10 (IQR 3-6). For specific measures to avoid bias, the reporting of randomisation was stated in 46% of experiments whereas 42% reported the blinded assessment of outcome.

In total 187 experiments were reported for infarct volume representing 2332 animals and 192 experiments were reported for neurobehavioural outcomes representing 2704 animals. Interestingly, where we stratified infarct volume data according to whether experiments were randomised or not, we found significantly higher estimates of efficacy in non-randomised studies. We did not find an impact of blinded assessment of outcome or allocation concealment.

We assessed experimental data for the prevalence of publication bias across both structural and functional outcomes. For structural outcomes we identified publication bias using Egger regression and Funnel plot asymmetry and Trim and fill identified one missing study. For functional outcomes, Egger regression did not suggest publication bias however time and fill suggested 52 missing studies.

We identified a number of aspects of methodology which significantly impacted upon observed effect size. For structural outcomes, the use of the immunosuppressant cyclosporine A was associated with greater improvements and the use of autologous opposed to allogeneic stem cells was also associated with greater improvements. Further, we identified that moderation of cells overall was associated with improvements in effect. For functional outcomes, the use of the immunosuppressant cyclosporine was also associated with greater improvements and the use of allogeneic opposed to autologous stem cells was also associated with greater improvements. Similar to structural outcomes, the moderation of stem cells was associated with significantly greater improvements in effect size.

In summary, we identified a number of weaknesses in the use of stem cells in experimental stroke. Measures to avoid potential bias were not frequently reported and there was substantial publication bias identified within the 117 studies. Results associated methodological variation with differences in observed effect size further demonstrating the need to perform experiments relevant to the clinical setting.

8.2: Systematic survey across a year in the Journal of Cerebral Blood Flow and Metabolism (JCBFM)

The failure to translate experimental findings from bench to bedside has been a prominent issue across medical discipline in recent years. Due to the prominence of the issue in cerebrovascular research, concerns have been raised regarding the quality and validity of experimental cerebrovascular studies. Therefore, we set out to assess study design, statistical analyses, and general experimental reporting over a year of original articles within the JCBFM. My specific role was to extract the data across all publications which were subsequently directly used in the output within the publication.

JCBFM articles from 2008 were subject to a pre-specified checklist which addresses issues across the design, age and statistics and reporting of experiments conducted (Figure 8.1 for study design questions). A total of 193 publications were published in the JCBFM year of 2008 of which 95 (49%) report animal studies, 49 (25%) report in vitro experiments, 34 (18%) report human studies, 8 (4%) were review articles and 29 (15%) articles which were of other types. We therefore took 156 original experimental studies forward to checklist assessment.

Results identified that while 97% reported the aim or purpose only 30% of publications stated a primary research hypothesis. Across publication identified measures to avoid bias such as randomisation, allocation concealment and blinding

were reported in less than 20% of publications and only 1% of studies reported sample size calculations or power analyses.

Category	*Question*
Design	
1	Was a primary/research hypothesis stated?
1a	Was an aim/purpose of study stated?
2	Was the design randomized? (Dirnagl, 2006)
3	Was allocation concealed?
4	Was outcome assessed blinded?
5	Was a statement about sample size given? (e.g., *a priori* power analysis) (Altman, 2002)
6	Was study design stated? (Andersen, 1990)
7	Were inclusion and exclusion criteria stated? (Altman *et al*, 1983; Andersen, 1990)

Figure 8.1: 15 principle questions were included in the systematic survey of the JCBFM of which 7 are demonstrated within the study design category. Questioned addressed aspects of study design, analysis and statistics and reporting.

For the reporting of analyses and statistics, we identified that wherever present 81% of publications used appropriate approaches and tests. For reporting variance, more than 90% of publications stated error on results of which 46% use standard error of the mean, 49% use standard deviation and 4% use conference intervals. 9% of publications did not state the variance reported.

In summary this work identifies issues in the conduct and reporting of experimental studies in a wider context and is likely to be a reliable representative of published neurological research. Similar to work in AD, the lack of: measures to avoid bias (blinding, randomisation), sample size calculations and fundamental study methodologies are both prevalent and concerning.

8.3 Exercise in experimental stroke

In recent years the benefits of regular exercise have been proposed as a preventative and therapeutic intervention across a range of neurological disorders including Alzheimer's disease. In focal ischemia there have been similar associations, where exercise is thought to reduce the risk of stroke and smaller infarcts. However, the mechanisms by which this occurs are poorly defined and there is little consensus as to which dose would be most beneficial or whether benefits would continue after the stroke has occurred. A considerable body of literature exists within animal models of focal ischemia and questions such as these were the focus of a meta-analysis conducted which I was involved with. Working alongside colleagues my role was to extract data from the identified publications, perform analyses and help write the manuscript.

Our results revealed that the use of exercise either pre or post ischemic stroke is associated with statistically significant reductions in infarct volume. Furthermore, animals exercised either pre or post ischemic stroke perform significantly better on tests of neurobehavioural function than animals receiving no exercise. Exercise appeared to be more advantageous when administered prior to, compared with after ischemic stroke, both in terms of its effect on reducing infarct volume and facilitating the recovery of neurobehavioural function.

In accordance with similar systematic reviews of animal models of focal ischemia, I found the reporting of study quality items infrequent. While the relationship between study quality and effect size in this dataset was unclear, there remains a substantial presence of publication bias for neurobehavioural outcomes.

Our stratified analyses suggest that both model- and exercise-specific methodology can influence observed outcomes. Examples of these included: type of ischemia and method of induction (model specific) alongside whether exercise was forced or voluntary or the mode of exercise itself (exercise specific). Further, meta-regression suggested that reductions in infarct volume were greatest when exercise was started before or soon after ischaemic stroke as opposed taking place much later after a stroke.

This work provides the first systematic review and meta-analysis of the use of exercise in animal models of focal cerebral ischemia. In summary, I found significant structural and behavioural benefits of exercise regardless of whether exercise was initiated prior to or after ischemic stroke. Despite such findings, the reported study quality was concerning, as was the evidence of publication bias within the described literature. Similar to issues in AD, investigators designing future experiments of pre- and post- ischemic exercise must be careful to consider what is practical for the clinical setting.

8.4 An online reporting facility for published data

Across pathological and neurobehavioural data I identified extensive publication bias and the creation of an online reporting facility for trials in preclinical AD (past and present) would be a significant step to address this. During the course of my PhD studies I have begun the process of developing an online reporting facility in collaboration with the Alzheimer's Drug Discovery Foundation (ADDF).

As part of the grant application for this, I have designed a user interface which allows users to choose a desired transgenic model group, outcome, intervention, dose or age of administration or assessment range (Figure 8.2). The online database is designed to help inform those conducting both preclinical and clinical trials in AD with the capacity to: (i) summarise existing data (Figure 8.3) and (ii) perform live meta-analyses to ascertain the likelihood of clinical efficacy (Figure 8.4).

While the data included in this thesis provides a systematic overview of interventions tested in transgenic models up until January 2009 I appreciate that the field is fast developing. I plan to expand to increase the relevance and scope of data collected by: (i) updating this dataset and perform monthly updates to ensure the database is current and (ii) extracting data across interventions tested across all pre-clinical AD animal models. This system would provide a comprehensive and novel resource in order to maximise the use of existing data in pre-clinical AD.

One concern of such a system which must be taken into account is that individual companies may wish to keep their development plans and studies secret. For example, smaller companies may have few incentives to share previous experimental research with competitors. Therefore it could be that facilitating different levels of study documentation would encourage more participation.

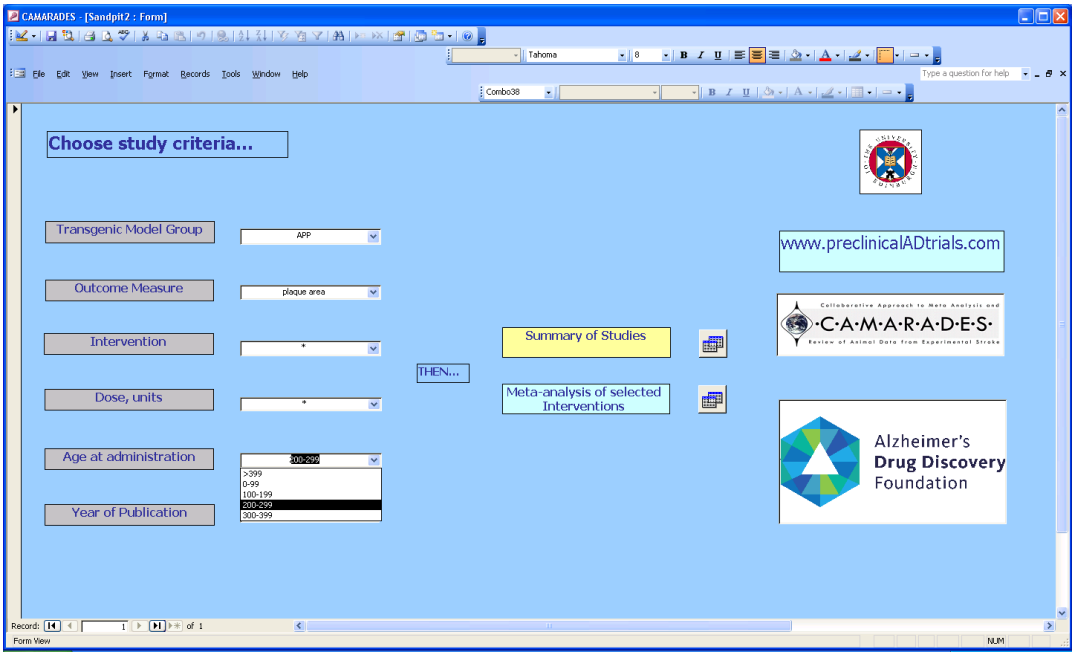

Figure 8.2: I designed a front end user interface for an online database of preclinical trials in Alzheimer's disease which will provide summaries or meta-analyses of data selected. Users will be able to specify data according to transgenic model group, outcome measure, intervention, dose, units, age at administration and year of publication.

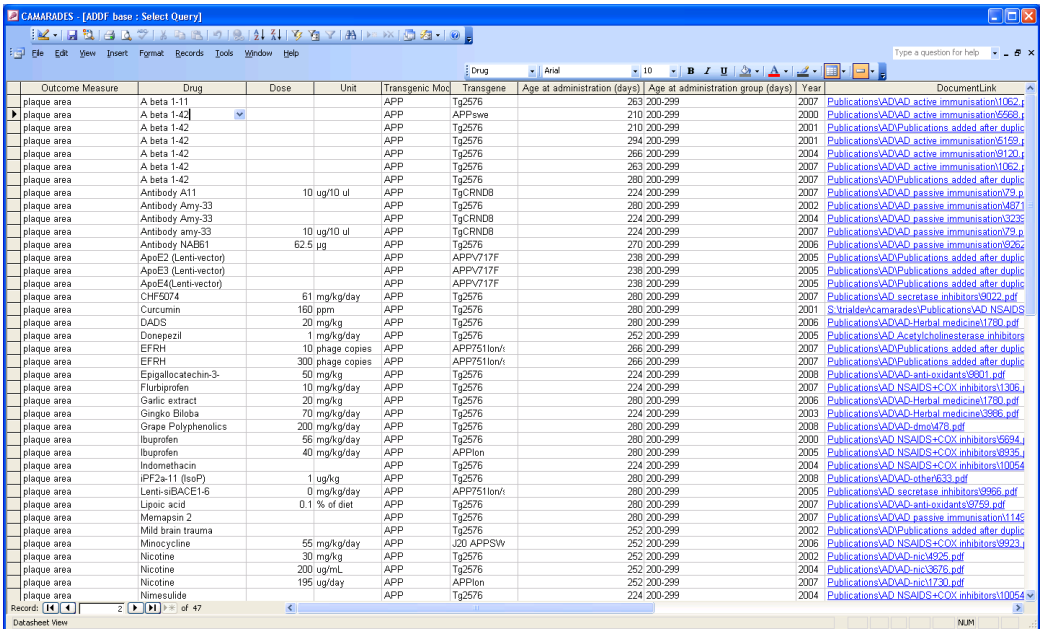

Figure 8.3: Users can summarise existing data according to: intervention tested, dose, transgenic model, age at administration, year of publication and link to publication.

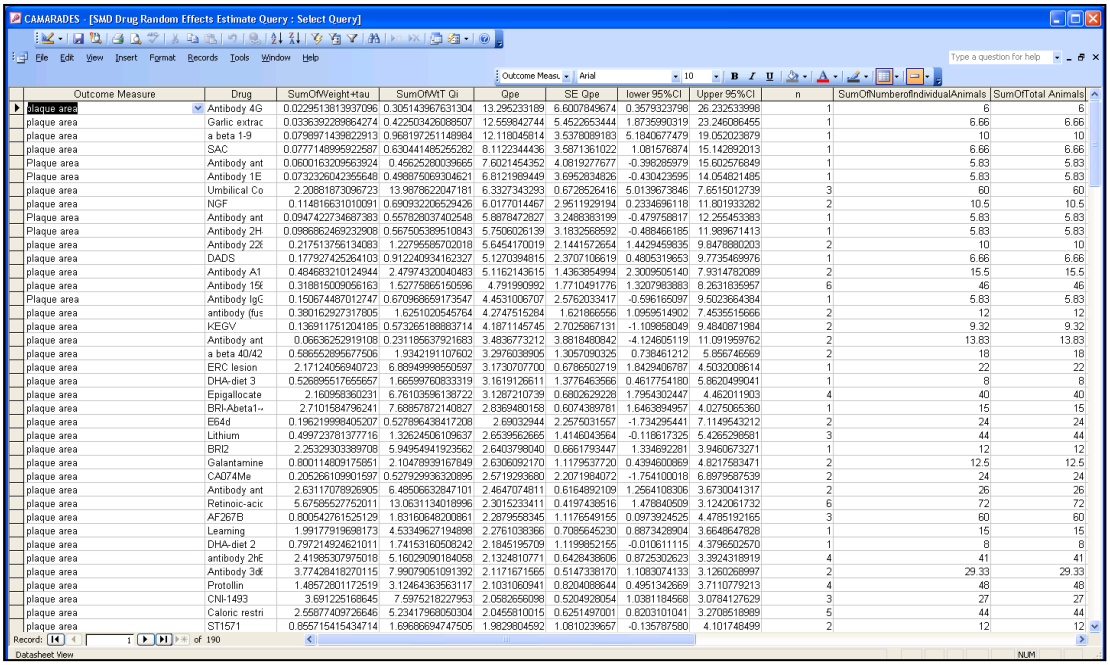

Figure 8.4: Users can also summarise existing data using meta-analysis techniques. Estimates will be provided as standardised mean difference estimates alongside the number of animals, and upper and lower 95 % confidence limits.

Chapter 9: General Discussion

The need for efficacious interventions capable of slowing, stopping or reversing Alzheimer's disease symptoms looks certain to increase in the years ahead. The aims of this thesis were to inform translational failure through the use of systematic review and meta-analysis on interventions tested in transgenic mouse models of the condition. In this final chapter I discuss key findings which include; (i) study methodology, (ii) study quality, (iii) interventions, (iv) publication bias, (v) limitations and (vi) concluding remarks.

In AD (and across neuroscience) the research community is becoming increasingly aware of critical shortcomings within pharmaceutical structures; drug discovery is high risk and long. It is estimated that 93% of all clinically tested CNS interventions fail to make it to the marketplace (7% worse than the market average) and for those which do, it takes an average of 12.6 years (Pangalos et al., 2007).

Academia and industry cannot afford to invest indefinitely in AD without realistic prospects of return and examining pre-clinical data is only part of the translational road block. Insights may be found by scrutinising failed AD clinical trial data, or by combining preclinical data synthesis insights and clinical practicalities together as demonstrated in hypothermia in stroke (van der Worp et al., 2010). Such multidisciplinary approaches allow rational trial design based on empirical data and are thus likely to increase our chances of identifying clinical efficacy.

9.1 Study methodology

The methodological variation present in studies is clearly extensive; particularly with respect to models used and the age at which interventions are administered and outcomes assessed. I was able to quantify the impact on a number of methodological aspects including: transgenic model group, age, sex, and inspect study design features within MWM experiments.

Collectively, the empirical evidence suggests the transgenic model used has an impact on the efficacy of interventions, particularly for pathological outcomes, (stratifying by transgenic model proved significant for 4 out of 6 outcomes). Interestingly, this was not observed for neurobehavioural results where differences between transgenic model groups were found in only two of six paradigms. Such trends may reflect different spectrums and magnitudes of AD pathologies caused by transgenes (e.g. the Tg2576 mouse does not capture tau pathology) whereas behavioural deficits are ultimately similar. Considering that authors are three times more likely to report pathological as opposed to neurobehavioural outcome, most data are vulnerable to those differences between transgenic models. Factoring that few interventions are tested in more than one transgenic model (24 % [84/357]) we may increase external validity of pre-clinical studies if interventions can demonstrate pathological efficacy across a number of transgenic models. This process could be aided through multi-centre animal trials similar to those planned in experimental stroke (multi-PART).

I identified a number of relationships when assessing the impact of age on outcome measures. In agreement with recent literature, experiments were conducted relatively early in the mouse lifespan and it was reassuring that neurobehavioural effects were smaller at earlier ages of administration and assessment (Zahs and Ashe, 2010). To understand this relationship further, I assessed whether neurobehavioural deficits changed over time within control animals. Overall, the presence of a transgene was associated with significantly worsened neurobehaviour at all ages assessed, but not in an age dependent manner.

Defining transgenic model phenotypes (particularly with respect to behaviour) has caused controversy in recent years with some studies suggesting that transgenic mice have no observable behavioural deficits (Deacon et al., 2008, Westerman et al., 2002). While our own data have reflected such concerns, in house meta-analysis studies of transgenic data elsewhere have demonstrated the complexities of ascertaining a direction of impact for neurobehaviour over time. Despite this, experimental data (and indeed the clinical phenotype) suggest that neurobehaviour deficits worsen with age (Reed et al., 2010). Our differences observed may be attributed to combining control data from different laboratories, transgenic models and behavioural paradigms, frequently with low power. There are also significant weaknesses in calculating effect size using SMD (see limitations) which must be taken into account across all analyses. Thus while increases in neurobehavioural intervention efficacy over time do not coincide with an increased magnitude of control animal behavioural deficits, results should be interpreted with caution.

For amyloid beta 40 and 42 intervention administration and assessment in older animals and longer durations between administration and assessment were associated with smaller intervention effects. Where I assessed the magnitude of transgene pathologies I identified that amyloid beta levels reduced as the mice age, in contrast to findings elsewhere that amyloid species increase over time (Kawarabayashi. et al., 2001). Further investigation is warranted to try and improve our understanding of whether it is the sensitivity of the approach taken which implies such a relationship or whether amyloid beta levels do reduce as the transgenic mice age.

For outcomes regarding neurodegeneration estimates of efficacy were smaller in older ages of administration and assessment but stratifying data did not prove statistically significant. Where I examined APP mice the magnitude of neurodegeneration showed a modest increase over time which would be expected considering in clinical AD cell loss increases with advancing disease stage. The increasing presence of neurodegeneration within control animals does not coincide with improved intervention efficacy (if anything data were suggestive of smaller estimates of efficacy at later time points) and reiterates that to prevent neurodegeneration, early intervention is required.

For tau outcomes, the impact of age on intervention efficacies and magnitude of transgene effect were overall inconclusive. Similarly, data on cellular infiltrates did

not demonstrate a direction of effect for intervention analyses overall, or for the transgene effect.

Collectively across age related analyses, it is clear that the age at which interventions are administered and outcomes assessed can impact on observed outcome. Therefore, declaring whether interventions are being tested as preventative or therapeutic strategies in preclinical trials is crucial to minimise overzealous interpretation of preclinical data. Recently published ADDF guidelines recommend such measures (Shineman et al., 2011), and across experimental science it is absolutely imperative that we can demonstrate efficacy under those conditions which reflect the clinical setting.

For sex analyses, analyses conducted were inconclusive. For pathological outcomes, males were associated with higher estimates of efficacy for four out of six outcomes but these were frequently marginal, and there was considerable overlapping of confidence limits. For neurobehavioural outcomes female transgenic mice were associated with greater improvements than males, however the limitations of meta-analyses were evident as estimates of efficacy for both sexes (i.e. males and females) were considerably lower. There is a considerable proportion of literature which identifies differences between male and female transgenic mice and it could be that our results are inconclusive because I have amalgamated different transgenes together within a single transgenic model group.

For neurobehavioural experiments, it is clear that the MWM has become the gold standard memory test: 64% (165/259) of all neurobehavioural experiments reported changes from the paradigm. Within the probe phase of the MWM I observed smaller estimates of efficacy at higher water temperatures. Considering that the paradigm requires a natural drive for mice to leave the water, it could be that colder water temperatures provide a greater degree of negative reinforcement.

Strengths and weaknesses arise when using any neurobehaviour paradigm and differences between groups in the MWM can differ according to the methodology used (Vorhees and Williams, 2006). However, reducing the potential impact of methodological influence altogether is complex: empirical evidence suggests that animal experiments results will differ even when standardised (Crabbe et al., 1999, Richter et al., 2009) and further, systematic variation present across preclinical studies is an asset for external validity (Richter et al., 2010).

Therefore, it may be advantageous to embrace the idiosyncrasy of experimental research. We may wish however, to advance our understanding of how specific methodologies may influence observed differences and consider adjusting estimates of efficacy before embarking on clinical trials. What remains critical is that we can contextualise findings, which at present could be strengthened by testing wild type mice as a transgene negative controls and/or making previous in house experimental data available.

9.2 Study quality

The lack of reporting of fundamental study quality items was concerning,: less than 1 in 5 studies reported blinded assessment of outcome or random allocation to group and no studies performed a sample size calculation. Such findings are relatively similar to animal models of other neurological diseases (Vesterinen et al., 2010, Sena et al., 2010a, Rooke et al., 2011). For pathological outcomes the relationship between study quality and effect was relatively inconsistent. Biologically, we might expect that valid hypothetical relationships would be reflected across all pathologies, which did not occur. For neurobehavioural experiments, the majority of blinded and randomised experiments reported smaller estimates of effect but did not prove statistically significant overall. Such results could reflect that neurobehavioural experiments are more susceptible to influence from such biases and one interpretation could be that the presence of fundamental study quality items should be performed as a precautionary measure.

When interpreting the impact of study quality items such as blinding it is important to keep in mind that findings may often represent a proxy for another part of the study (i.e. it is not clear whether the observed differences are a direct measure of the conduct of the studies opposed to a more overall measure of general conduct and reporting). Further, blinding or randomisation were generally based on explicit statements regarding this, but were open to further scrutiny.

The absence of sample size calculations has been identified across experimental neuroscience, well beyond experimental AD (Vesterinen et al., 2011). Systematic review in multiple sclerosis has identified that animal experiments were insufficiently powered to assess differences between groups and across preclinical AD the lack of sample size calculations was reflected by low group sizes (Vesterinen et al., 2010). While it is accepted that spontaneous transgenic model attrition and local availability can pose major challenges to laboratory groups, it remains crucial for internal validity that I use sufficient numbers of animals to detect differences between groups. Such issues have been addressed in published experimental guidelines; the ARRIVE guidelines recommend (at the very least) an explanation of how experimental numbers arose (Kilkenny et al., 2010) and recently published guidelines from the ADDF promote the use of sample size calculation in experimental design (Shineman et al., 2011).

I retrospectively inspected an additional study quality item concerning the use of a wild type group, the majority of paradigms (4 out of 6) reported smaller estimates of effect where wild type animals were present such findings did not reach statistical significance. Even if findings are coincidental, behavioural paradigms between laboratory groups are almost always unique (alongside experimental design). Therefore defining differences between wild type and transgenic animals is useful to: (i) ensure measurable differences between wild type and transgenic phenotypes exist and, (ii) put intervention effects in context with maximal improvement. Again, such measures are recommended by the ADDF guidelines (Shineman et al., 2011).

9.3 Observed relationships within and between outcomes

Our analyses suggested a number of relationships regarding outcome measures in particular with respect to amyloid beta and plaque burden. For example, I identified strong correlations between the different staining techniques used to assess plaque burden and changes in amyloid beta 40 were generally reflective of changes in amyloid beta 42. This implies that the clearance of plaques correlate well with the clearance of amyloid species and further that the clearance of amyloid beta species (at least with respect to amyloid beta 40 and 42) is generally not peptide length specific. Meta-regression analyses also identified that changes in plaque pathology correlated strongly with changes in tau and particularly prominently with changes in neurodegeneration. Such results reflect relationships identified from the amyloid cascade hypothesis previously in transgenic mice (Love, 2001, Urbanc et al., 2002)

Thus, it can be tempting to speculate that numerous results provide evidence in favour of the amyloid cascade hypothesis (Hardy, 2003, Pike et al., 1993). However, I must be cautious as our analyses do not imply causation- it could be that two outcomes are affected simultaneously either directly or indirectly through an intermediary. Across those outcome measure relationships identified (both within pathology, and between pathology and neurobehaviour), multivariate meta-

regression or path analysis may help further our understanding of relationships identified.

For neurobehavioural experiments, analyses identified a relatively strong correlation between the acquisition and probe phase within the use of the MWM. Where I analysed data from the acquisition phase at different time points in isolation, I identified that as the acquisition phase progressed, observed changes became more reflective of those observed in the probe phase. Such results suggest that probe phase performance can be explained, at least in part by acquisition phase performance. Understanding how the methodology of the MWM impacts on detecting differences between groups has been investigated previously, where researchers were able to identify that 'proximity to platform' within the probe phase was the most sensitive outcome measure (Maei et al., 2009). Here, our results suggest that there is a strong relationship between the acquisition and probe phase. Such hypotheses emphasise the need for both the acquisition and probe results to be reported both in full, regardless of whether efficacy is demonstrated or not.

Overall, data suggested 20% of the variation in neurobehaviour could be explained by variation in pathological outcomes. Where I looked more specifically within pathologies I found that improvements in plaque burden and amyloid beta 40 and 42 correlated with changes in neurobehaviour (<30%). Such relationships have been described in APP Tg2576 mice previously (Westerman et al., 2002) but I did not have sufficient data to inspect associations between specific oligomers species which

have been frequently suggested to provide associations with behavioural performance (Lesne et al., 2006).

For tau pathologies it was surprising that I did not identify a relationship between changes in structural outcome and change in functional outcomes as this is often perceived to be a better predictor of neurobehaviour than amyloid (Walsh and Selkoe, 2004). What our results may reflect are that: (i) few experiments (and models) report changes in tau and neurobehaviour and, (ii) for studies which do, there appears to be little consensus on how to measure changes in tau (e.g. selecting the number of specific phosphorylation sites). There may be benefits if the field could reach a consensus on which tau phosphorylation sites are the most important.

Interestingly, the strongest pathological predictor of changes in neurobehaviour was neurodegeneration, a finding similar to a number of clinical studies (Terry et al., 1991, Sze et al., 1997). While I must accept that data overall were limited (20 experiments) this finding was also shown within APP transgenic models in isolation. Thus, data suggest that if I are measuring pathologies as surrogate measures of neurobehaviour within AD models, markers of neurodegeneration may prove particularly reliable predictors.

9.4 Interventions

Across the 357 individual interventions identified, the depth of information available for any single intervention was extremely limited. Experiments are generally conduced with relatively low group sizes and only one in four interventions were tested in more than one transgenic model. In truth, studies were more indicative of proof of concept as opposed to studies conducted to reliably quantify the likelihood of clinical efficacy.

Hypotheses frequently drive experimental research and this was well represented within specific outcomes assessed for given interventions. For example, of the 22 experiments which report pathological outcomes on the anti-inflammatory intervention LY-411575, 22 report changes in amyloid beta 40 whereas no publications reported changes in tau or neurodegeneration. Further, until the AD community definitively establishes which pathology (or pathologies) causes memory loss, clinical trial design is likely to benefit from establishing portfolios of evidence across a range of pathological outcomes. Using existing data on specific interventions I are able to (i) identify outcomes where few or no experiments have been conducted and (ii) where data do exist, use cumulative meta-analysis to guide where experiments are needed most. It is accepted that I face biological limits to the range and depth by which AD models capture symptoms. Nevertheless, synthesising evidence across a range of AD outcomes is likely to provide greater

depth in the external validity of intervention efficacy and further, has the potential highlight potential combination therapies.

9.5 Implications of publication bias

Publication bias was identified using all techniques extensively across pathological and neurobehavioral datasets, regardless of: brain region, outcomes or transgenic model group. Findings are similar to other disease models (such as experimental stroke and MS) where preclinical datasets have also indicated publication bias.

It is disconcerting that AD experiments provide yet another example of the relentless drive to selectively publish efficacious interventions (Sena et al., 2010b). The 'everything works approach' is not only biologically improbable but encourages the use of limited resources on false leads, in an industry where the odds are already slender. The point that publication bias exists indiscriminately across experimental medicine suggests that current structures in the pharmaceutical industry need to be reconsidered. It is likely that the solution lies in a multidisciplinary approach where authors, journal editors and funding bodies collectively ensure neutral and negative studies are reported and published in full.

Some early signs of change may already be upon us. For example, there are now journals which only accept neutral or negative results (e.g. Journal of negative results in biomedicine) and it is becoming increasingly common for universities to develop and share open data repositories (Sandercock, 2012). I find it encouraging to have made significant progress in developing a comprehensive open data repository for preclinical studies of AD and would encourage similar systems to be designed across experimental medicine to maximise the use of existing data.

9.6 Limitations

Analyses conducted within this thesis are post hoc and one must interpret all findings as empirically guided hypotheses. Within analyses, I have made substantial efforts to take account of differences between transgenic models expressed, however I was not able to quantify the impact of zygosity or promoter and our analyses face considerable challenges balancing specificity and power. Throughout this work I have designed analyses around the spread of the data identified, not a hypothesis, outcome or individual transgenic model.

While this approach maximises power, this could cause us to miss crucial subtleties within data analysed. For neurobehavioural analyses, performing analyses on individual paradigms does not take into account specific cognitive processes (and/or those brain regions involved). This is clearly a very important area, and it could be possible to categorise data in terms of the types of neuropsychological assessments made. However, while I considered categorising data according to specific processes, this requires assumptions to be made on the strategies used (which there may be no consensus on) and our own analyses have suggested that within the MWM multiple processes may be at play simultaneously. Further, I have attempted to reduce the impact of such weaknesses by conducting behavioural analyses on the overall data, as it is unlikely that a given clinical trial would require paradigm specific improvements.

I identified articles using a systematic search as a methodology which reduce bias but it is still possible that I have missed publications which should be included. We did not use Explode, focus or truncation codes in the search conducted and this may have increased the number of publications included overall. Further, data are likely to be missing due the effects of publication bias. If analyses concerning study quality and characteristics were conducted including such experiments then results may substantially differ.

For the calculation of effect sizes there are two main approaches used; standardised mean difference and normalised mean difference. For our datasets analyses the standardised mean difference was used almost universally across the dataset. While this technique is good for combining data from different scales I cannot always assume that observed relationships are consistently reflective of true biological efficacies. For example, if the mean values in a given cohort became broader over time, effect sizes would suggest that efficacy decreased which is somewhat deceptive. Additionally, a particular weakness of animal studies is that the variance used is an estimate of an infinite population rather than a true measurement and thus small study effects may also impact on observed results

Overall it must be accepted that theoretical relationships identified may not necessarily be true if I used alternative techniques (e.g. meta-regression/stratified meta-analysis, or specific calculation of effect size). Thus the collective use of meta-

analysis in animal models needs a degree of refining, in particular to determine the sensitivities of possible approaches.

Throughout the analyses conducted, statistical power was lost due to missing or unclear data regarding: the number of animals used variance and also study methodology (e.g. age at assessment). While I emailed 16 authors for further information in order to address such issues it is plausible that this may directly impact on observed relationships.

9.7 Concluding remarks

The aims of this thesis were to describe and explore interventions tested in transgenic mouse models of Alzheimer's disease in order to provide evidence to develop evidence based Good Laboratory Practice guidelines. Analyses identified: (i) pre-clinical studies are characteristically diverse and few studies report fundamental study quality items (e.g. blinding, randomisation), (ii) study characteristics and study quality impact on the observed efficacy, and (iii) extensive publication bias is present across transgenic mouse model literature. Additionally, I have identified a number of interesting hypotheses both within and between outcomes measures which may be informative to trial design and disease hypotheses. Collectively, empirical data suggest that we cannot take evidence from preclinical trials at face value and further demonstrate the utility of systematic review and meta-analysis. The message from preclinical studies is clear: experiments at the bench must begin, and end, at the bedside. Furthermore, if we are to accelerate AD drug discovery it remains imperative that the wider scientific community maximises the use of existing data from pre-clinical trials to inform, educate and ultimately improve our translational hit rate. The words of C.S Lewis are as true now as ever,

"Failures are finger posts on the road to achievement."

Appendix I: Publications identified from Systematic review

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Appendix II: Reported Study Quality

Author	Year	1	2	3	4	5	Total Study Quality Score
Abramowski	2008	-	-	-	+	-	1
Adlard	2005	-	-	-	+	-	1
Adlard	2008	-	-	-	+	-	1
Ambree	2006	+	-	-	+	-	2
Anderson	2005	-	-	-	+	-	1
Arendash	2001	-	-	-	-	-	0
Arendash	2004	-	-	-	-	-	0
Arendash	2006	-	+	-	+	-	2
Arendash	2007	-	+	-	-	-	1
Arranz	2008	-	-	-	-	-	0
Asai	2006	-	-	-	+	-	1
Asami-Odaka	2005	-	-	-	-	-	0
Asberom	2007	-	-	-	-	-	0
Asuni	2006	+	-	-	+	-	2
Asuni	2007	-	-	-	-	-	0
Augustin	2008	-	+	-	+	-	2
Augustin	2009	-	+	-	+	-	2
Austin	2003	+	-	-	-	-	1
Bacher	2008	+	-	-	+	-	2
Bacskai	2002	-	-	-	-	-	0
Bales	2006	-	-	-	+	+	2
Bard	2003	+	-	-	-	-	1
Barten	2005	-	-	-	+	-	1
Battaglia	2003	-	-	-	-	-	0
Bayer	2003	-	-	-	+	-	1
Becker	2007	+	-	-	+	+	3
Berardi	2007	-	-	-	+	-	1
Bergamaschini	2004	+	-	-	+	-	2
Bergstrom	2008	-	-	-	-	-	0
Bergstrom	2008	-	-	-	-	-	0
Best	2007	+	-	-	+	-	2
Billings	2005	-	-	-	-	-	0
Billings	2007	-	-	-	-	-	0
Bissette	2005	-	-	-	-	-	0
Boado	2007	-	-	-	+	-	1
Boimel	2008	-	-	-	-	-	0
Boissonneault	2008	-	-	-	-	-	0

Author	Year	1	2	3	4	5	Total Study Quality Score
Bowers	**2005**	-	-	-	+	-	1
Boyett	**2003**	-	-	-	+	-	1
Brendza	**2005**	-	-	-	+	+	2
Burbach	**2007**	+	-	-	-	-	1
Bussiere	**2004**	-	-	-	-	-	0
Butovsky	**2006**	-	-	-	+	+	2
Butovsky	**2007**	-	-	-	+	-	1
Buttini	**2005**	+	-	-	+	-	2
Caccamo	**2006**	+	-	-	-	-	1
Caccamo	**2007**	-	-	-	+	-	1
Calon	**2004**	-	+	-	-	-	1
Calon	**2005**	-	+	-	+	-	2
Cannella	**2008**	+	-	-	+	-	2
Cao	**2007**	-	-	-	+	-	1
Cao	**2008**	-	-	-	+	-	1
Cao	**2009**	-	-	-	+	-	1
Capsoni	**2002**	-	-	-	-	-	0
Capsoni	**2004**	-	-	-	-	-	0
Carro	**2006**	-	-	-	+	+	2
Carroll	**2007**	-	+	-	+	-	2
Carty	**2006**	-	-	-	+	+	2
Carty	**2008**	-	-	-	-	-	0
Carty	**2008**	-	-	-	-	-	0
Casadesus	**2006**	+	+	-	-	-	2
Cavalli	**2007**	-	-	-	-	-	0
Chang	**2004**	-	-	-	+	-	1
Chang	**2007**	-	-	-	-	-	0
Chauhan	**2002**	-	-	-	-	-	0
Chauhan	**2003**	-	-	-	-	-	0
Chauhan	**2003**	-	-	-	+	-	1
Chauhan	**2004**	-	-	-	-	-	0
Chauhan	**2004**	-	-	-	-	-	0
Chauhan	**2004**	-	-	-	-	-	0
Chauhan	**2005**	-	-	-	-	-	0
Chauhan	**2005**	-	-	-	-	-	0
Chauhan	**2006**	-	-	-	+	-	1
Chauhan	**2007**	-	-	-	-	-	0
Chauhan	**2007**	-	-	-	-	-	0
Chauhan	**2007**	-	-	-	-	-	0
Chen	**2006**	-	-	-	+	-	1
Chen	**2007**	+	-	-	-	-	1

Author	Year	1	2	3	4	5	Total Study Quality Score
Cherny	2001	+	+	-	+	+	4
Cho	2003	-	-	-	+	-	1
Choi	2007	-	-	-	+	-	1
Chu	2008	-	+	-	-	-	1
Comery	2005	-	-	-	-	-	0
Costa	2007	-	-	-	+	-	1
Cracchiolo	2007	-	+	-	+	-	2
Czirr	2007	-	-	-	+	-	1
Das	2001	+	-	-	-	-	1
DaSilva	2006	+	-	-	+	-	2
De Rosa	2005	-	-	-	-	-	0
Dedeoglu	2004	-	-	-	-	-	0
DeMattos	2001	-	+	-	-	-	1
DiCarlo	2001	-	+	-	-	-	1
Dickstein	2006	-	-	-	+	-	1
Dinamacra	2008	-	-	-	+	-	1
Dineley	2007	-	-	-	+	-	1
Ding	2008	+	+	-	+	-	3
Dodart	2002	+	-	-	+	+	3
Dodart	2005	-	-	-	+	-	1
Dong	2004	+	-	-	+	-	2
Dong	2005	-	-	-	-	-	0
Dong	2008	-	+	-	+	+	3
Dovey	2001	-	-	-	-	-	0
Du	2005	-	-	-	-	+	1
Dvir	2006	-	-	-	+	-	1
El-Amouri	2008	-	-	-	-	-	0
Elesber	2004	-	-	-	-	-	0
Elesber	2006	-	-	-	+	-	1
Engel	2006	-	-	-	-	-	0
Esposito	2008	+	+	-	-	-	2
Etcheberrigaray	2004	-	-	-	+	-	1
Ethell	2006	-	-	-	+	-	1
Facchinetti	2006	-	-	-	+	-	1
Fan	2007	-	-	-	+	-	1
Fenili	2007	-	-	-	+	-	1
Frazer	2008	-	+	-	+	-	2
Frenkel	2003	-	-	-	-	-	0
Frenkel	2005	+	-	-	+	+	3
Frenkel	2008	+	-	-	+	-	2
Frye	2008	+	+	-	+	-	3

Author	Year	1	2	3	4	5	Total Study Quality Score
Fukuchi	2006	-	-	-	+	-	1
Fuso	2008	-	-	-	+	-	1
Garcia	2008	-	-	-	+	-	1
Garcia-Alloza	2006	-	-	-	+	-	1
Garcia-Alloza	2007	-	-	-	+	-	1
Garcia-Alloza	2007	-	-	-	-	-	0
Gaugler	2005	+	-	-	-	-	1
George	2004	+	+	-	+	-	3
Gervais	2007	+	-	-	-	-	1
Ghosh	2008	-	-	-	-	-	0
Goldstein	2007	-	-	-	-	-	0
Gong	2004	+	-	-	+	+	3
Gong	2006	+	-	-	+	-	2
Gortz	2008	+	-	-	+	-	2
Green	2005	-	+	-	+	-	2
Green	2006	-	-	-	+	-	1
Green	2007	+	-	-	-	-	1
Green	2008	-	-	-	+	-	1
Greig	2005	-	+	-	+	+	3
Halagappa	2007	-	-	-	-	-	0
Han	2008	-	-	-	-	-	0
Hara	2004	-	+	-	+	-	2
Hara	2006	-	+	-	-	-	1
Hartman	2005	-	-	-	-	-	0
Hartman	2006	-	-	-	-	-	0
Hasegawa	2003	-	-	-	-	-	0
Heikkinen	2004	-	-	-	+	-	1
Hellstrom-Lindahl	2004	-	-	-	-	-	0
Hemming	2007	-	-	-	+	-	1
Hemming	2007	+	-	-	+	+	3
Heneka	2005	-	-	-	+	-	1
Herber	2004	-	-	-	-	-	0
Herber	2007	-	-	-	-	-	0
Herring	2008	+	-	-	+	-	2
Hirko	2007	+	-	-	+	-	2
Hofmeister	2002	-	-	-	-	-	0
Holcomb	2006	-	-	-	+	-	1
Hooijmans	2007	-	-	-	+	-	1
Hook	2008	-	-	-	-	+	1
Horikoshi	2004	-	-	-	+	-	1
Hu	2008	-	+	-	-	-	1

Author	Year	1	2	3	4	5	Total Study Quality Score
Hussain	2007	-	-	-	-	-	0
Hutter-Paier	2004	+	+	-	-	-	2
Hwang	2006	-	-	-	-	-	0
Hyde	2006	-	-	-	+	-	1
Imbimbo	2007	-	-	-	+	-	1
Imbimbo	2007	-	-	-	+	-	1
Inoue	2006	-	-	-	-	-	0
Iwata	2004	+	-	-	+	-	2
Jacobsen	2008	-	-	-	-	+	1
Jankowsky	2005	-	-	-	+	-	1
Jantzen	2002	+	-	-	-	-	1
Janus	2000	+	-	-	-	+	2
Jensen	2005	+	-	-	+	-	2
Jeong	2006	-	-	-	+	-	1
Joseph	2003	-	-	-	-	-	0
Josien	2007	-	-	-	-	-	0
Karlnoski	2008	-	-	-	+	+	2
Kim	2004	-	-	-	+	-	1
Kim	2005	-	-	-	+	-	1
Kim	2007	+	-	-	-	-	1
Kim	2007	-	-	-	+	-	1
Kim	2008	-	-	-	+	-	1
Kim	2008	-	-	-	+	-	1
Kitazawa	2005	-	-	-	-	-	0
Klausner	2008	+	+	-	+	-	3
Koenigsknecht-Talboo	2008	-	-	-	+	-	1
Koldamova	2005	-	-	-	+	-	1
Kotilinek	2002	-	-	-	-	-	0
Kotilinek	2008	-	-	-	-	+	1
Kukar	2007	+	-	-	+	-	2
Kulic	2006	-	-	-	+	-	1
Kulkarni	2008	-	-	-	+	-	1
Lanz	2005	-	-	-	+	-	1
Lanz	2008	-	-	-	-	+	1
Lavie	2004	-	+	-	-	-	1
Lazarov	2005	-	-	-	+	-	1
Le Corre	2006	-	-	-	+	+	2
Lebson	2008	-	-	-	-	-	0
Lee	2004	+	+	-	+	+	4
Lee	2005	-	-	-	+	-	1
Lee	2006	+	-	-	+	-	2

Author	Year	1	2	3	4	5	Total Study Quality Score
Leighty	2008	-	-	-	-	-	0
Lemere	2003	-	-	-	+	-	1
Levites	2006	-	-	-	+	-	1
Levites	2006	+	-	-	-	+	2
Li	2004	-	-	-	-	-	0
Li	2006	-	+	-	+	-	2
Li	2006	-	-	-	-	-	0
Li	2007	-	-	-	+	-	1
Li	2008	-	-	-	-	-	0
Lim	2000	+	+	-	-	-	2
Lim	2001	-	-	-	-	-	0
Lim	2005	-	-	-	-	-	0
Liskowsky	2006	-	-	-	+	-	1
Liu	2002	-	+	-	+	-	2
Liu	2007	-	-	-	-	-	0
Lombardo	2003	-	-	-	-	-	0
Ma	2006	-	+	-	+	-	2
Maier	2006	-	-	-	+	-	1
Malm	2007	-	-	-	-	-	0
Mamikonyan	2007	-	-	-	-	-	0
Marr	2003	-	-	-	-	-	0
Marr	2003	-	-	-	-	-	0
Marr	2004	-	-	-	-	-	0
Martinez-Coria	2008	-	-	-	-	-	0
Marutle	2007	-	-	-	-	+	1
Matsubara	2003	-	-	-	+	-	1
Matsuoka	2003	+	-	-	-	-	1
Matsuoka	2007	-	-	-	-	-	0
Matsuoka	2008	-	-	-	-	-	0
McBriar	2008	-	-	-	-	-	0
Mckee	2008	-	-	-	-	+	1
McLaurin	2006	-	+	-	+	+	3
Melnikova	2006	-	-	-	+	-	1
Michaelis	2006	-	-	-	-	-	0
Minkevicience	2004	-	-	-	+	-	1
Mizoroki	2007	-	-	-	+	-	1
Moechars	1998	-	-	-	-	-	0
Mohajeri	2002	+	-	-	-	-	1
Mohajeri	2004	+	-	-	-	-	1
Mohajeri	2004	+	-	-	-	-	1
Morgan	2000	+	-	-	-	-	1

Author	Year	1	2	3	4	5	Total Study Quality Score
Mori	2006	+	+	-	+	-	3
Morihara	2005	-	-	-	-	-	0
Mottin	2002	-	-	-	-	-	0
Mouri	2007	-	-	-	+	-	1
Movsesyan	2008	+	-	-	+	+	3
Mucke	2002	-	-	-	-	-	0
Muhs	2007	-	+	-	+	+	3
Nakashima	2004	+	+	-	+	-	3
Nakashima	2005	+	+	-	+	-	3
Nelson	2007	-	-	-	+	-	1
Nichol	2007	+	-	-	+	-	2
Nichol	2008	-	-	-	+	+	2
Nicolakakis	2008	+	-	-	+	-	2
Nicolau	2002	-	-	-	-	-	0
Nikolic	2007	-	-	-	-	+	1
Nikolic	2008	+	-	-	+	+	3
Noble	2005	-	-	-	+	-	1
Nordberg	2002	+	-	-	-	-	1
Oddo	2004	-	-	-	+	-	1
Oddo	2005	+	-	-	-	-	1
Oddo	2006	-	+	-	-	-	1
Oddo	2006	-	-	-	+	-	1
Oddo	2008	+	+	-	+	-	3
Oksman	2006	+	-	-	+	-	2
Okura	2006	+	-	-	+	+	3
Okura	2008	+	-	-	+	-	2
Onozuka	2008	+	+	-	+	-	3
Page	2008	-	-	-	+	-	1
Parachikova	2008	-	-	-	+	-	1
Paris	2003	-	-	-	-	-	0
Paris	2004	-	-	-	-	-	0
Park	2003	+	-	-	+	-	2
Park	2006	-	-	-	-	-	0
Patel	2005	-	+	-	-	-	1
Paul	2007	-	-	-	+	+	2
Pedersen	2004	-	-	-	+	-	1
Pedersen	2006	+	-	-	+	-	2
Peretto	2005	-	-	-	+	-	1
Permanne	2002	-	-	-	-	-	0
Petanceska	2002	-	-	-	-	-	0
Petrushina	2007	+	-	-	+	-	2

Author	Year	1	2	3	4	5	Total Study Quality Score
Petrushina	**2008**	+	-	-	-	-	1
Pihlaja	**2008**	-	-	-	+	-	1
Pillay	**2008**	-	+	-	+	-	2
Plattner	**2006**	-	-	-	+	-	1
Prada	**2007**	-	-	-	+	-	1
Prasad	**2007**	-	-	-	-	-	0
Pratico	**2002**	+	+	-	+	-	3
Pugh	**2007**	-	-	-	+	+	2
Puglielli	**2005**	-	-	-	+	+	2
Qin	**2008**	-	+	-	+	-	2
Qing	**2008**	-	-	-	+	+	2
Qu	**2004**	-	-	-	-	+	1
Qu	**2006**	-	-	-	+	-	1
Qu	**2007**	-	-	-	+	-	1
Quinn	**2003**	-	-	-	+	-	1
Quinn	**2005**	-	-	-	+	-	1
Quinn	**2007**	-	-	-	-	+	1
Racke	**2005**	-	-	-	-	-	0
Rakover	**2007**	-	-	-	-	-	0
Refolo	**2000**	-	-	-	-	-	0
Refolo	**2000**	+	-	-	-	-	1
Refolo	**2001**	+	-	-	-	-	1
Ren	**2007**	-	-	-	+	-	1
Rezai-Zadeh	**2008**	+	-	-	+	-	2
Ribes	**2006**	-	-	-	+	-	1
Ribes	**2008**	-	-	-	+	-	1
Ribes	**2008**	-	-	-	+	-	1
Richter	**2008**	-	-	-	+	-	1
Riddell	**2007**	-	-	-	-	-	0
Rockenstein	**2002**	-	-	-	-	-	0
Rockenstein	**2002**	-	-	-	+	-	1
Rockenstein	**2003**	+	-	-	-	+	2
Rockenstein	**2004**	-	-	-	-	-	0
Rockenstein	**2005**	-	-	-	+	-	1
Rockenstein	**2006**	-	-	-	+	-	1
Rockenstein	**2007**	-	-	-	-	-	0
Rockenstein	**2007**	-	-	-	+	-	1
Rockenstein	**2007**	+	-	-	+	-	2
Rosario	**2006**	-	-	-	-	-	0
Rosenmann	**2007**	-	-	-	-	+	1
Ryder	**2003**	-	-	-	+	-	1

Author	Year	1	2	3	4	5	Total Study Quality Score
Sabbagh	2008	-	-	-	+	-	1
Sadowski	2004	-	+	-	-	-	1
Sadowski	2006	-	+	-	+	+	3
Sankaranarayanan	2008	-	-	-	+	-	1
Sastre	2006	-	-	-	-	+	1
Schafer	2007	-	-	-	+	-	1
Schenk	1999	-	-	-	-	-	0
Schilling	2008	-	-	-	+	+	2
Scholtzova	2008	+	-	-	+	-	2
Schroeter	2008	+	-	-	-	+	2
Schultz	2004	-	-	-	-	-	0
Seabrook	2004	-	-	-	+	-	1
Seabrook	2006	-	-	-	+	+	2
Seabrook	2006	-	-	-	+	-	1
Seabrook	2007	-	-	-	+	-	1
Senechal	2008	-	-	-	-	-	0
Seubert	2008	-	-	-	-	-	0
Sheng	2002	-	+	-	+	-	2
Shie	2002	-	+	-	+	-	2
Shim	2007	-	-	-	+	-	1
Shim	2008	-	-	-	+	-	1
Shineman	2008	-	-	-	+	-	1
Sigurdsson	2001	+	-	-	+	-	2
Sigurdsson	2004	+	-	-	+	-	2
Singer	2005	+	-	-	+	+	3
Snow	2002	-	-	-	-	-	0
Snow	2004	-	-	-	-	-	0
Soderman	2008	+	-	-	+	-	2
Solomon	2004	-	-	-	-	-	0
Solomon	2007	-	+	-	-	-	1
Sood	2007	-	-	-	+	-	1
Spencer	2008	-	-	-	+	-	1
Stackman	2003	+	-	-	+	-	2
Stahl	2006	-	-	-	+	-	1
Stein	2004	-	-	-	+	-	1
Stoltenberg	2007	+	-	-	+	-	2
Su	2003	-	-	-	-	-	0
Su	2004	-	+	-	+	-	2
Sung	2003	-	+	-	+	-	2
Sung	2004	+	+	-	+	-	3
Tabira	2008	-	+	-	-	-	1

Author	Year	1	2	3	4	5	Total Study Quality Score
Takata	2007	-	-	-	+	-	1
Tamura	2005	-	-	-	-	-	0
Tchantchou	2007	-	-	-	+	-	1
Tian	2008	-	-	-	-	-	0
Town	2002	+	-	-	-	-	1
Trinchese	2008	+	-	-	+	+	3
Tsai	2007	-	-	-	+	+	2
Tucker	2006	-	-	-	-	-	0
Tucker	2008	-	-	-	+	-	1
Um	2008	-	-	-	+	-	1
Unger	2006	-	+	-	+	-	2
Uryu	2002	+	-	-	+	-	2
Van Dam	2005	+	+	-	+	-	3
Van Dam	2006	-	+	-	+	-	2
Van Dam	2008	-	+	-	+	-	2
Van Groen	2008	-	-	-	+	-	1
Van Vickle	2007	-	-	-	-	-	0
Vasilevko	2007	+	-	-	+	+	3
Vehmas	2001	+	-	-	+	-	2
Velliquette	2005	-	+	-	+	-	2
Vloeberghs	2008	-	-	-	+	-	1
Volmar	2000	-	-	-	-	-	0
Wang	2005	-	+	-	+	-	2
Wang	2006	-	+	-	-	-	1
Wang	2007	-	-	-	+	-	1
Wang	2007	-	+	-	+	+	3
Wang	2008	-	-	-	+	-	1
Weiner	2000	-	+	-	+	+	3
Westerman	2002	-	-	-	-	+	1
Wilcock	2001	-	+	-	-	-	1
Wilcock	2003	-	-	-	-	-	0
Wilcock	2004	-	-	-	-	-	0
Wilcock	2006	-	-	-	-	-	0
Wilcock	2007	-	-	-	+	-	1
Windisch	2004	-	-	-	-	-	0
Windisch	2007	-	-	-	-	-	0
Wisniewski	2004	-	-	-	-	-	0
Wisor	2005	-	-	-	+	-	1
Wolf	2006	-	+	-	+	-	2
Wong	2004	-	-	-	+	-	1
Yamamoto	2005	-	-	-	-	-	0

Author	Year	1	2	3	4	5	Total Study Quality Score
Yan	**2003**	-	-	-	-	-	0
Yang	**2005**	-	-	-	-	-	0
Yang	**2008**	-	-	-	+	-	1
Yoshiike	**2008**	-	-	-	+	+	2
Youm	**2005**	-	-	-	-	-	0
Zamora	**2006**	-	-	-	+	+	2
Zhang	**2003**	-	-	-	+	-	1
Zhang	**2004**	-	-	-	-	-	0
Zhang	**2005**	+	-	-	-	-	1
Zhang	**2006**	-	-	-	-	-	0
Zhang	**2006**	-	+	-	+	-	2
Zhang	**2007**	-	-	-	-	-	0
Zhao	**2004**	-	+	-	+	-	2
Zheng	**2002**	+	-	-	-	-	1
Zheng	**2004**	-	-	-	+	-	1
Zheng	**2006**	-	-	-	+	-	1
Zhou	**2003**	-	-	-	-	-	0
Zhu	**2004**	-	-	-	-	-	0
Zou	**2007**	+	-	-	-	-	1
Zou	**2008**	-	-	-	+	-	1
Zurbriggen	**2005**	+	+	-	-	-	2

Appendix II: Table explains the number of publications which reported each study quality item: (1) blinded assessment of outcome, (2) random allocation to group, (3) sample size calculation, (4) compliance with animal welfare legislation and (5) statement regarding potential conflicts of interest.

Appendix III: Study Characteristics of included studies

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Boyett et al. (2003)	C1q	N/A		multiple	U	APPPS	>336 and <504.1	>336 and <504.1	Plaque area	10
Butovsky et al. (2007)	Glatiramer acetate	N/A		SubCut	U	APPPS	<168.1	>168 and <336.1	Plaque area	6
Cancino et al. (2008)	ST1571	12.5	mg/kg	Iperitoneal	U	APPPS	>168 and <336.1	>168 and <336.1	Acquisition	6
									Neurodegeneration	6
									TAU	6
Cao et al. (2007)	Sucrose Sweetened Water	10	%	Oral	M	APPPS	<168.1	>168 and <336.1	Acquisition	14
									Amyloid beta 40	14
									Amyloid beta 42	14
									Plaque area	14
									Probe	14
									T/Y maze	15
Carroll et al. (2007)	Estrogen	0.25	mg	SubCut	F	3xTgAD	<168.1	<168.1	Plaque area	14
									TAU	14
									T/Y maze	14
	Progesterone	25	mg	SubCut	F	3xTgAD	<168.1	<168.1	Plaque area	14
									TAU	14
									T/Y maze	14
Carty et al. (2006a)	Endothelin Converting Enzyme (ECE)	N/A		iCranial	U	APPPS	<168.1	>168 and <336.1	Plaque area	16
Cavalli et al. (2007)	memoquin	7	mg/kg/day	Iperitoneal	U	other	>336 and <504.1	>336 and <504.1	Plaque area	8
									TAU	8
	memoquin	7	mg/kg/day	Iperitoneal	U	other	<168.1	>168 and <336.1	Plaque area	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									TAU	8
	memoquin	7	mg/kg/day	Iperitoneal	U	other	<168.1	<168.1	TAU	8
Chauhan (2007)	Antibody A11	10	ug/10 ul	intraventriclular	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
									Plaque area	7.5
	Antibody Amy-33	10	ug/10 ul	intraventriclular	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
									Plaque area	7.5
Cho et al. (2003)	Exercise	2520	mins	N/A	U	other	>168 and <336.1	>336 and <504.1	Amyloid beta 42	6
									Probe	6
Dedeoglu et al. (2004)	Compound XH1	25	mg/kg	Oral	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	8
DiCarlo et al. (2001)	LPS	N/A		iHippocampus	B	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	9
	LPS	N/A		iHippocampus	B	APPPS	>336 and <504.1	>336 and <504.1	Plaque area	13
Dodart et al. (2005)	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 42	8
	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	8
	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	7.5
	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	7.5
	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	9
	apoE3 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 42	10
	apoE3 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	10
	apoE4(Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	9
	apoE4(Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 42	9

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	apoE4(Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	7.5
	apoE4(Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	7.5
	apoE4(Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	10
	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	11.67
	apoE2 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	11.67
	apoE3 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	10.67
	apoE3 (Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	10.67
	apoE4(Lenti-vector)	N/A		iHippocampus	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42 Plaque area	7.667 7.667
Dong et al. (2004)	Isolation Stress	N/A		Iperitoneal	B	APP	<168.1	<168.1	Fear conditioning Neurodegeneration Plaque area	16 16 10
Frazer et al. (2008)	A beta 1-42	N/A		SubCut	M	3xTgAD	<168.1	>168 and <336.1	TAU	9
	A beta 1-42	N/A		SubCut	M	3xTgAD	<168.1	>168 and <336.1	TAU	9
Frye & Walf (2008)	Progesterone	N/A		SubCut	F	APPPS	<168.1	>168 and <336.1	NORT T/Y maze	10 10
Fukuchi et al. (2006)	Antibody scFv	N/A		multiple	U	APP	>336 and <504.1	<168.1	Plaque area	12
Fuso et al. (2008)	B-vitamin Deprivation	N/A		Oral	B	APP	<168.1	<168.1	Amyloid beta 40 Amyloid beta 42 Plaque area	30 30 20
	B-vitamin Deprivation	N/A		Oral	B	APP	<168.1	<168.1	Amyloid beta 40 Amyloid beta 42 Plaque area	30 30 20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	B-vitamin Deprivation	N/A		Oral	M	APP	<168.1	<168.1	Acquisition	19
Gong et al. (2006)	Uch-L1	0.03	g/kg	Iperitoneal	B	APPPS	<168.1	<168.1	Amyloid beta 42	12
	Uch-L1	0.03	g/kg	Iperitoneal	B	APPPS	<168.1	<168.1	Amyloid beta 42	15
	Uch-L1	0.03	mg/kg	Iperitoneal	B	APPPS	<168.1	<168.1	Fear conditioning	28
	Uch-L1	0.03	mg/kg	Iperitoneal	B	APPPS	<168.1	<168.1	Fear conditioning	34
	LDN-57444	0.4	mg/kg	Iperitoneal	B	APPPS	<168.1	<168.1	Fear conditioning	38
Green et al. (2006)	Dexamethasone	1	mg/kg	Iperitoneal	M	3xTgAD	<168.1	<168.1	Amyloid beta 40	9
									Amyloid beta 42	9
	Dexamethasone	5	mg/kg	Iperitoneal	M	3xTgAD	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	16
									TAU	6
	Dexamethasone	5	mg/kg	Iperitoneal	M	3xTgAD	>336 and <504.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8
Green et al. (2005)	Estrogen	N/A		Unknown	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	15
									Amyloid beta 42	14.33
Greig et al. (2005)	N-phenethnorcymserine(PEC)	3	mg/kg/day	Iperitoneal	M	APPPS	<168.1	<168.1	Amyloid beta 40	24
									Amyloid beta 42	24
Heikkinen et al. (2004)	Estrogen	N/A		SubCut	F	APPPS	<168.1	<168.1	Acquisition	26
								>168 and <336.1	Probe	26
									RAWM	26
									T/Y maze	26

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Estrogen	N/A		SubCut	F	APPPS	<168.1	<168.1	Amyloid beta 40	19
									Amyloid beta 42	19
								>168 and <336.1	Acquisition	30
									RAWM	30
									T/Y maze	30
	Estrogen	N/A		SubCut	F	APPPS	<168.1	>168 and <336.1	Acquisition	38
									Probe	30
								>336 and <504.1	RAWM	34
									T/Y maze	34
	Estrogen	N/A		SubCut	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	19
									Amyloid beta 42	19
									Plaque area	16
	Estrogen	N/A		SubCut	F	APPPS	<168.1	>336 and <504.1	Probe	38
	Estrogen	N/A		SubCut	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	25
									Amyloid beta 42	25
	Estrogen	N/A		SubCut	F	APPPS	<168.1	>336 and <504.1	Amyloid beta 40	29
									Amyloid beta 42	29
									Plaque area	29
Horikoshi et al. (2004)	Antibody 82E1	10	mg/kg	Iperitoneal	U	APP	>336 and <504.1	>504	Amyloid beta 42	5
									Plaque area	5
Hu et al. (2008)	A beta 1-15	N/A		multiple	U	APP	<168.1	>336 and <504.1	Acquisition	10.66
									Probe	10.67
	A beta 36-42	N/A		multiple	U	APP	<168.1	>336 and <504.1	Acquisition	10.66
									Probe	10.67

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	A beta 1-42	N/A		multiple	U	APP	<168.1	>336 and <504.1	Acquisition	10.66
									Probe	10.67
Hwang et al. (2006)	Furin	N/A		Icortex	U	APP	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	10
	Furin	N/A		Icortex	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	10
									Amyloid beta 42	10
Jacobsen et al. (2008)	PAZ-417	20	mg/kg/day	Oral	M	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	10
									Amyloid beta 42	10
	PAZ-417	20	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	16
									Amyloid beta 42	16
	PAZ-417	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Fear conditioning	10.67
	PAZ-417	30	mg/kg/day	Oral	M	APP	<168.1	<168.1	Fear conditioning	10.67
	PAZ-417	100	mg/kg/day	Oral	M	APP	<168.1	<168.1	Fear conditioning	10.67
	PAZ-417	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Fear conditioning	16
	DAPT	100	mg/kg/day	Oral	M	APP	<168.1	<168.1	Fear conditioning	16
Kim et al. (2008a)	BRI2	N/A		IVentricular	B	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12
	BRI-Abeta1-40	N/A		IVentricular	B	APP	<168.1	<168.1	Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	15
	BRI2	N/A		IVentricular	B	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
	BRI2-del244-266	N/A		IVentricular	B	APP	<168.1	<168.1	Amyloid beta 40	17

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	17
									Plaque area	17
Kitazawa et al. (2005)	LPS	0.5	mg/kg	Iperitoneal	B	3xTgAD	<168.1	<168.1	Amyloid beta 40	16
									Amyloid beta 42	16
									Plaque area	10
									TAU	10
Kulic et al. (2006)	A beta 1-42	N/A		Iperitoneal	F	Tau	>168 and <336.1	>168 and <336.1	TAU	18
Liskowsky & Schliebs (2006)	Scolopamine Hydorbromide	2	mg/kg/day	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	12
									Amyloid beta 42	12
Matsubara et al. (2003)	Melatonin	1.5	mg/day	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	8
	Melatonin	1.5	mg/day	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	12
									Amyloid beta 42	13.5
	Melatonin	1.5	mg/day	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	14
									Amyloid beta 42	14
	Melatonin	1.5	mg/day	Oral	U	APP	<168.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12
Melnikova et al. (2006)	celecoxib	N/A		Oral	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	14
									Amyloid beta 42	14
									Plaque area	14
									T/Y maze	17
	celecoxib	N/A		Oral	M	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40	14
									Amyloid beta 42	14

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	14
									T/Y maze	17
	celecoxib	N/A		Oral	M	APPPS	>168 and <336.1	>168 and <336.1	T/Y maze	32
Mohajeri et al. (2004)	A beta 1-42	1	ul/350 uM	Icortex	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	7
									Plaque area	8
	A beta 1-42	35	ul/350 uM	Icortex	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	8
									Plaque area	7
Mohajeri, Wollmer, & Nitsch (2002)	A beta 1-42	N/A		iCranial	U	APP	<168.1	>168 and <336.1	Plaque area	8
Mouri et al. (2007)	A beta 1-42	N/A		Oral	F	APP	>168 and <336.1	>336 and <504.1	Acquisition	28
									Amyloid beta 40	16
									Amyloid beta 42	16
									Fear conditioning	28
									NORT	28
									Plaque area	13
									Probe	28
Nichol et al. (2008)	Exercise	N/A	EE	N/A	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	11
									Amyloid beta 42	11
									Cellular infiltrates	12.75
Oddo et al. (2006b)	Antibody 20.1 (monoclonal)	N/A		Iperitoneal	U	3xTgAD	>504	>504	Amyloid beta 40	15
									Amyloid beta 42	15
									Fear conditioning	15
									TAU	15
									T/Y maze	15
	Antibody 20.1 (monoclonal)	N/A		Iperitoneal	U	3xTgAD	>504	>504	Amyloid beta 40	20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	20
									Fear conditioning	20
									TAU	20
									T/Y maze	20
	A beta 1-42	N/A		SubCut	U	3xTgAD	>504	>504	Amyloid beta 40	15
									Amyloid beta 42	15
									Fear conditioning	15
									TAU	15
									T/Y maze	15
Park et al. (2006)	Nogo-66 receptor -ecto-Fc	0.27	mg/kg/day	SubCut	U	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40	16
									Amyloid beta 42	16
									Cellular infiltrates	16
									Neurodegeneration	16
									Plaque area	16
									RAWM	16
Paul, Strickland, & Melchor (2007)	Tranexamic acid	100	U/day	SubCut	U	APP	<168.1	<168.1	Cellular infiltrates	6
									Plaque area	6
	Ancrod	4	mg/day	SubCut	U	APP	<168.1	<168.1	Plaque area	5
Pratico et al. (2002)	Aluminium	2	mg/kg/diet	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 40	20
									Amyloid beta 42	20
									Plaque area	12
Refolo et al. (2000)	High Cholesterol	N/A		Oral	M	APPPS	<168.1	<168.1	Amyloid beta 40	14
									Amyloid beta 42	14
									Plaque area	16

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Ribes et al. (2008a)	Aluminium	17	mg/kg/day	Oral	M	APP	<168.1	>168 and <336.1	Acquisition	16
									Amyloid beta 40	16
									Amyloid beta 42	16
									Neurodegeneration	16
									Probe	16
Ribes et al. (2008b)	Aluminium	0.09	mg/g	Oral	U	APP	not known	not known	Amyloid beta 40	14
									Amyloid beta 42	14
	Aluminium	0.09	mg/g	Oral	U	APP	not known	not known	Neurodegeneration	6
Richter et al. (2008)	Exercise	N/A		N/A	M	APP	<168.1	<168.1	NORT	22
									Plaque area	21
Sabbagh et al. (2008)	nicotine	200	ug/mL	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 40	40
									Amyloid beta 42	40
									Cellular infiltrates	40
									Neurodegeneration	40
Sadowski et al. (2004)	Amyloid beta-12-28P	100	µmol/L	Iperitoneal	U	APPPS	<168.1	<168.1	Plaque area	12
Sheng, Price, & Koliatsos (2002)	ERC lesion	N/A		Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40	22
									Amyloid beta 42	22
									Plaque area	22
Shie et al. (2002)	High Cholesterol	N/A		Oral	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
	High Cholesterol	N/A		Oral	F	APP	<168.1	>168 and <336.1	Plaque area	8
Stein et al. (2004)	TTR antibody	N/A		SubCut	U	APP	>504	>504	Neurodegeneration	8
Stoltenberg et al. (2007)	Zinc deficiency	N/A		Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	18

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Su, Ryder, & Ni (2003)	H89	103	uM	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 42	20
Tsai, Tsai, & Shen (2007)	G-CSF	N/A		SubCut	M	APP	>168 and <336.1	>336 and <504.1	Acquisition	10
									Neurodegeneration	10
									Plaque area	10
Uryu et al. (2002)	Mild brain trauma	N/A		N/A	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	6
									Amyloid beta 42	6
			single	N/A	B	APP	>168 and <336.1	>336 and <504.1	Acquisition	19.5
	Mild brain trauma	N/A		N/A	B	APP	>168 and <336.1	>336 and <504.1	Acquisition	17.5
									Amyloid beta 40	6
									Amyloid beta 42	6
	Mild brain trauma	N/A		N/A	B	APP	>168 and <336.1	>168 and <336.1	Plaque area	6
	Mild brain trauma	N/A		N/A	B	APP	>168 and <336.1	>168 and <336.1	Plaque area	6
	Mild brain trauma	N/A		N/A	B	APP	>168 and <336.1	>336 and <504.1	Plaque area	6
	Mild brain trauma	N/A		N/A	B	APP	>168 and <336.1	>336 and <504.1	Plaque area	6
Velliquette, O'Connor, & Vassar (2005)	Kainic acid	30	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	Kainic acid	30	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	Kainic acid	30	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	2-deoxyglucose(2DG)	1	g/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	2-deoxyglucose(2DG)	1	g/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	2-deoxyglucose(2DG)	1	g/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	3-Nitropropionic acid (3NP)	100	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	3-Nitropropionic acid (3NP)	100	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	3-Nitropropionic acid (3NP)	100	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Insulin	18	U/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	Insulin	18	U/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
	Insulin	18	U/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	5
Wilcock et al. (2001)	A beta 1-42	N/A		SubCut	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates	12
	A beta 1-42	N/A		SubCut	U	APP	>336 and <504.1	>504	Cellular infiltrates	10
	A beta 1-42	N/A		SubCut	U	APP	>168 and <336.1	>336 and <504.1	Cellular infiltrates	12
Windisch et al. (2004)	MDVFMKGLSMAKE	5	mg/day	INasal	U	APP	not known	not known	Acquisition	12
Yoshiike et al. (2008)	Picrotoxin	N/A		Iperitoneal	M	APPPS	>168 and <336.1	>168 and <336.1	Neurodegeneration	12
									NORT	12
									Probe	12
Zheng et al. (2002)	Estrogen	5	ug/mL	Oral	F	APPPS	<168.1	<168.1	Amyloid beta 40	6
									Amyloid beta 42	6
	Estrogen	1.7	mg	SubCut	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	11
									Amyloid beta 42	11
	Estrogen	5	mg	SubCut	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	12
Zou et al. (2007)	captopril	30	mg/kg/day	Oral	M	APP	<168.1	>336 and <504.1	Amyloid beta 40	26
									Amyloid beta 42	26
									Plaque area	26
Koenigsknecht-Talboo et al. (2008)	IgG2b	N/A		Iperitoneal	U	APP	>504	>504	Cellular infiltrates	5
	M3D6	N/A		Iperitoneal	U	APP	>504	>504	Cellular infiltrates	5
	M3D6	N/A		Iperitoneal	U	APP	>504	>504	Cellular infiltrates	8
	M3D6	N/A		Iperitoneal	U	APP	<168.1	<168.1	Cellular infiltrates	8
	m3D6 Fab Fragments	N/A		Iperitoneal	U	APP	>504	>504	Cellular infiltrates	5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	mHJ5.1	N/A		Iperitoneal	U	APP	>504	>504	Cellular infiltrates	5
van Groen et al. (2008)	D3	0.25	mg/pump	iHippocampus	U	APPPS	<168.1	<168.1	Cellular infiltrates	15
									Plaque area	15
	D1	N/A		iHippocampus	U	APPPS	<168.1	<168.1	Cellular infiltrates	14
									Plaque area	14
Spencer et al. (2008)	Neprilysin	2	µl	multiple	U	APP	<168.1	>336 and <504.1	Acquisition	16
									Neurodegeneration	16
									Plaque area	16
									Probe	16
									TAU	16
Oddo et al. (2008)	A beta 1-42	N/A		iHippocampus	B	3xTgAD	<168.1	>336 and <504.1	Amyloid beta 40	9
									Amyloid beta 42	9
									TAU	9
	CHIP expressing lentivirus	3	ul	iHippocampus	B	3xTgAD	>504	>504	TAU	8
	CHIP expressing lentivirus	3	ul	iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	TAU	8
Qing et al. (2008)	Valproic acid	30	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	60
	Valproic acid	30	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	24
	Valproic acid	30	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	60
			mg/kg/day	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Acquisition	60
									Probe	60
	Valproic acid	30	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	60
	Valproic acid	30	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	60
	Valproic acid	30	mg/kg	Iperitoneal	U	APPPS	<168.1	<168.1	Plaque area	54

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Green et al. (2008)	Nicotinamide	200	mg/kg/day	Oral	U	3xTgAD	<168.1	>168 and <336.1	Acquisition	16
									Amyloid beta 40	16
									Amyloid beta 42	16
									Fear conditioning	16
									NORT	16
									Probe	16
									TAU	16
	Nicotinamide	200	mg/kg/day	Oral	U	3xTgAD	>504	>504	Amyloid beta 40	10
									Amyloid beta 42	10
									TAU	10
	Sodium butyrate	800	mg/kg/day	Oral	U	3xTgAD	>336 and <504.1	>336 and <504.1	Amyloid beta 40	16
									Amyloid beta 42	16
									TAU	16
Ding et al. (2008)	Retinoic-acid	20	mg/kg/day	Iperitoneal	M	APPPS	<168.1	>168 and <336.1	Acquisition	12
									Cellular infiltrates	12
									Neurodegeneration	12
									Plaque area	12
									Probe	12
Okura et al. (2008)	A beta (unspecified length)	50	ug/week	intramuscular	U	APP	<168.1	>336 and <504.1	Plaque area	6
	A beta (unspecified length)	50	ug/week	intramuscular	U	APP	<168.1	>336 and <504.1	Cellular infiltrates	7
									Plaque area	6
	A beta (unspecified length)	50	ug/week	intramuscular	U	APP	<168.1	>168 and <336.1	Cellular infiltrates	6
Dong et al. (2008)	Memantine	5	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Fear conditioning	14.67
									Neurodegeneration	14.67

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	14.67
	Memantine	10	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Fear conditioning	19.67
									Neurodegeneration	19.67
									Plaque area	19.67
	Memantine	20	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Fear conditioning	11.67
									Neurodegeneration	11.67
									Plaque area	11.67
Um et al. (2008)	Exercise	4850	mins	N/A	U	Tau	>336 and <504.1	>336 and <504.1	Amyloid beta 42	10
									Neurodegeneration	10
									Probe	10
Scholtzova et al. (2008)	Memantine	10	mg/kg/day	Iperitoneal	U	APPPS	<168.1	>168 and <336.1	Cellular infiltrates	14
									NORT	14
									Plaque area	14
Nicolakakis et al. (2008)	Pioglitazone	20	mg/kg/day	Oral	U	APP	>336 and <504.1	>336 and <504.1	Acquisition	8
									Amyloid beta 40	10
									Amyloid beta 42	10
									Cellular infiltrates	8
									Plaque area	10
									Probe	8
Carty et al. (2008)	Endothelin Converting Enzyme (ECE)	2	µl	iCranial	U	APPPS	<168.1	>168 and <336.1	Plaque area	16
Onozuka et al. (2008)	Nobiletin	10	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	17
									Amyloid beta 42	17
									Fear conditioning	16
									Plaque area	17

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Karlnoski et al. (2008)	Antibody D-2H6	3	mg/kg/week	Iperitoneal	U	APP	>504	>504	Cellular infiltrates Plaque area RAWM	6.667 6.667 6.667
	Antibody D-2H6	10	mg/kg/week	Iperitoneal	U	APP	>504	>504	Cellular infiltrates Plaque area RAWM	6.667 6.667 6.667
	Antibody D-2H6	30	mg/kg/week	Iperitoneal	U	APP	>504	>504	Cellular infiltrates Plaque area RAWM	6.667 6.667 6.667
Nikolic et al. (2008)	Umbilical Cord Blood Cells	N/A		Ivenous	B	APPPS	>168 and <336.1	>336 and <504.1	Cellular infiltrates Plaque area	20 20
Wang et al. (2008)	Grape Polyphenolics	200	mg/kg/day	Oral	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40 Amyloid beta 42	10 10
	Grape Polyphenolics	200	mg/kg/day	Oral	F	APP	<168.1	>168 and <336.1	Acquisition Probe	12 12
Gortz et al. (2008)	Environmental Enrichment	N/A		N/A	F	APP	<168.1	<168.1	NORT	13
Li et al. (2008)	A beta 16-20	3	nmol	iHippocampus	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates Neurodegeneration Plaque area	10 9.5 9.5
	A beta 16-22	0.3	nmol	iHippocampus	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates Plaque area	10.5 16.5
McKee et al. (2008)	Ibuprofen	375	ppm	Oral	U	3xTgAD	<168.1	>168 and <336.1	Acquisition Plaque area	10 10

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Probe	10
									TAU	10
Shineman et al. (2008)	SQ	2	mg/kg	intraventriclular	F	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6
									Amyloid beta 42	6
									Plaque area	7
	iPF2a-11 (IsoP)	1	ug/kg	intraventriclular	F	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6
									Amyloid beta 42	6
									Plaque area	8
El Amouri et al. (2008)	Neprilysin	3	µl	multiple	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	38
									Amyloid beta 42	38
									Cellular infiltrates	38
									Plaque area	38
									Probe	38
Van Dam, Coen, & De Deyn (2008)	Donepezil	0.27	mg/kg/day	SubCut	M	APP	<168.1	<168.1	Acquisition	14.5
									Probe	14.5
	Donepezil	0.58	mg/kg/day	SubCut	M	APP	<168.1	<168.1	Acquisition	14.5
									Probe	14.5
Sankaranarayanan et al. (2008)	Merk-3	30	mg/kg/day	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
	Merk-3	7.5	mg/kg/day	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	9
									Amyloid beta 42	9
	Merk-3	7.5	mg/kg/day	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	10

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Merk-3	30	mg/kg/day	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	9
									Amyloid beta 42	9
Windisch et al. (2007)	KEGV	5	mg/kg	INasal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	4.667
	KEGV	50	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	4.667
	SMAKEGV	5	mg/kg	INasal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	4.667
	SMAKEGV	50	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	4.667
	MDVFMKGLSMAKE	5	mg/kg	INasal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	4.667
	MDVFMKGLSMAKE	50	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	4.667
Kotilinek et al. (2008)	Ibuprofen	375	ppm	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	20.67
									Amyloid beta 42	20.17
									Probe	24.67
	Naproxen	375	ppm	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	20.67
									Amyloid beta 42	20.17
									Probe	23.67
	MF tricyclic	13	ppm	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	20.17
									Amyloid beta 42	20.67
									Probe	23.67
	Ibuprofen	375	ppm	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	16
	Ibuprofen	375	ppm	Oral	U	APP	<168.1	>168 and <336.1	Probe	32
									T/Y maze	32
	MF tricyclic	13	ppm	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	10
	Naproxen	375	ppm	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	10
Klausner et al. (2008)	Oxybutynin	3.75	mg/ml	Oral	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 42	9

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Oxybutynin	3.75	mg/ml	Oral	M	APPPS	<168.1	>168 and <336.1	Amyloid beta 42	8
Herring et al. (2008)	Environmental Enrichment	N/A		N/A	F	APP	<168.1	<168.1	Amyloid beta 40	18
									Amyloid beta 42	18
Yang et al. (2008)	Coenzyme Q10	1200	mg/kg/day	Oral	F	PS1	>336 and <504.1	>504	Amyloid beta 40	10
									Amyloid beta 42	10
Page et al. (2008)	MRK-560	3	mg/kg/day	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	4.5
									Amyloid beta 42	4.5
	GSM-1	3	mg/kg/day	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	GSM-1	10	mg/kg/day	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	GSM-1	30	mg/kg/day	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	MRK-560	3	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	4.5
									Amyloid beta 42	4.5
	GSM-1	3	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	GSM-1	10	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	GSM-1	30	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
Vasilevko et al. (2007)	A beta 1-42	100	µg	SubCut	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	A beta 1-11	50	µg	SubCut	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	7.5
	A beta 1-11	50	µg	SubCut	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	A beta 1-40	100	µg	SubCut	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
Nichol, Parachikova, & Cotman (2007)	Exercise	N/A		N/A	B	APP	>336 and <504.1	>336 and <504.1	RAWM	22
Petrushina et al. (2007)	A beta 1-11	N/A		SubCut	F	APP	>168 and <336.1	>504	Amyloid beta 40	19
									Amyloid beta 42	19
									Cellular infiltrates	19
									Plaque area	19
	A beta 1-42	N/A		SubCut	F	APP	>168 and <336.1	>504	Amyloid beta 40	10
									Amyloid beta 42	10
									Cellular infiltrates	10
									Plaque area	10
Chang et al. (2007)	Memapsin 2	N/A		SubCut	F	APP	<168.1	>336 and <504.1	Acquisition	13
									Amyloid beta 40	24
									Amyloid beta 42	24
									Plaque area	24
									Probe	13
	Memapsin 2	N/A		SubCut	F	APP	>168 and <336.1	>336 and <504.1	Acquisition	9
									Amyloid beta 40	17
									Amyloid beta 42	17
									Plaque area	17
									Probe	9

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Qu et al. (2007)	A beta 1-42	N/A		SubCut	U	APPPS	<168.1	>336 and <504.1	Amyloid beta 42 Cellular infiltrates Plaque area	12 12 12
Hirko et al. (2007)	Gelsolin	N/A		Ivenous	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	12.33
	Gelsolin	N/A		Ivenous	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates Plaque area	6 6
Ren et al. (2007)	40H-GTS-21	1	mg/kg	Iperitoneal	M	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	20
Asuni et al. (2007)	Tau379–408	N/A		SubCut	M	Tau	<168.1	<168.1	TAU	13
	Tau379–408	N/A		SubCut	M	Tau	<168.1	>168 and <336.1	TAU	12
	Tau379–408	N/A		SubCut	F	Tau	<168.1	<168.1	TAU	13
	Tau379–408	N/A		SubCut	F	Tau	<168.1	>168 and <336.1	TAU	12
	Tau379–408	N/A		SubCut	B	Tau	<168.1	>168 and <336.1	NORT	24
Garcia-Alloza et al. (2007a)	Curcumin	7.5	mg/kg/day	Ivenous	B	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40 Amyloid beta 42 Neurodegeneration	8 8 6
Berardi et al. (2007)	Environmental Enrichment	N/A		N/A	B	other	<168.1	>168 and <336.1	NORT Probe	24 24
	Environmental Enrichment	N/A		N/A	B	other	<168.1	>168 and <336.1	Plaque area TAU	22 24
Herber et al. (2007)	LPS	10	ug	Iperitoneal	B	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates	10.5
	LPS	10	ug	iCranial	B	APP	>336 and <504.1	>336 and <504.1	Plaque area	10.5
	Dexamethasone	5	mg/kg	Iperitoneal	B	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates Plaque area	10.5 10.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Prasad et al. (2007)	BMS-433796	30	umol/kg	Oral	U	APP	not known	not known	Amyloid beta 40	14
Chauhan & Sandoval (2007)	Garlic extract	0.2	%	Oral	U	APP	<168.1	>168 and <336.1	Acquisition	20
									Amyloid beta 40	20
									Amyloid beta 42	20
									Probe	20
									T/Y maze	20
	Garlic extract	0.2	%	Oral	U	APP	<168.1	>168 and <336.1	Acquisition	20
									Amyloid beta 40	20
									Amyloid beta 42	20
									Probe	20
									T/Y maze	20
Kukar et al. (2007)	Flurbiprofen	10	mg/kg/day	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	45
									Amyloid beta 42	45
									Plaque area	45
	Flurbiprofen	10	mg/kg/day	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	45
									Amyloid beta 42	45
	Flurbiprofen	10	mg/kg/day	Oral	U	APP	>336 and <504.1	>504	Amyloid beta 40	43
									Amyloid beta 42	43
									Plaque area	45
									Probe	28
	Flurbiprofen	10	mg/kg/day	Oral	U	APP	>168 and <336.1	>168 and <336.1	Probe	45
Mamikonyan et al. (2007)	Antibody anti-beta-11	2	copies	iHippocampus	U	3xTgAD	>504	>504	Plaque area	8
Muhs et al. (2007)	a beta 1-16	N/A		Iperitoneal	F	APPPS	<168.1	<168.1	NORT	7.5
	A beta 1-15	N/A		Iperitoneal	F	APPPS	<168.1	<168.1	NORT	7.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Zhang et al. (2007)	Soybean phosphatidylinositol	500	nM	iHippocampus	U	Tau	<168.1	<168.1	Neurodegeneration	4
	A beta 25-35	100	nM	iHippocampus	U	Tau	<168.1	<168.1	Neurodegeneration	4
	A beta 25-35	1	uM	iHippocampus	U	Tau	<168.1	<168.1	Neurodegeneration	4
Seabrook et al. (2006b)	A beta 40/42	N/A		multiple	U	APP	<168.1	>168 and <336.1	Amyloid beta 40 Amyloid beta 42 Plaque area	8 8 8
	A beta 1-15	N/A		multiple	U	APP	<168.1	>168 and <336.1	Amyloid beta 40 Amyloid beta 42 Plaque area	8 8 8
	A beta 1-15	N/A		multiple	U	APP	<168.1	>168 and <336.1	Amyloid beta 40 Amyloid beta 42 Plaque area	9 9 9
Carty et al. (2006b)	Antibody 2h6 (deglycosylated)	N/A		iCranial	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates Plaque area	6 6
	Antibody 2h6	N/A		iCranial	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates Plaque area	9 9
Nelson et al. (2007)	paroxetine	5	mg/kg/day	Iperitoneal	M	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40 TAU	10 10
	paroxetine	5	mg/kg/day	Iperitoneal	F	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40 TAU	10 10
	paroxetine	5	mg/kg/day	Iperitoneal	B	3xTgAD	<168.1	>168 and <336.1	Acquisition Probe	20 20
Seabrook et al. (2007)	A beta 1-15	N/A		INasal	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	10

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	10
									Plaque area	10
Costa et al. (2007)	Environmental Enrichment	N/A		N/A	B	APPPS	<168.1	<168.1	Acquisition	29.5
									Plaque area	16
									RAWM	30
	Environmental Enrichment	N/A		N/A	B	APPPS	<168.1	<168.1	Plaque area	22
	Rolipram	0.03	mg/kg/day	SubCut	U	APPPS	>168 and <336.1	>336 and <504.1	RAWM	9
Caccamo et al. (2007)	Lithium	N/A		Iperitoneal	U	3xTgAD	>336 and <504.1	>336 and <504.1	Amyloid beta 40	20
									Amyloid beta 42	20
									TAU	20
									T/Y maze	20
Green et al. (2007)	DHA-diet 1	1.3	per 100g	Oral	B	3xTgAD	<168.1	<168.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
									TAU	8.5
	DHA-diet 1	1.3	per 100g	Oral	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8
	DHA-diet 1	1.3	per 100g	Oral	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8.667
	DHA-diet 2	N/A		Oral	B	3xTgAD	<168.1	<168.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									TAU	8.75
	DHA-diet 2	N/A		Oral	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8
	DHA-diet 2	N/A		Oral	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8
	DHA-diet 3	N/A		Oral	B	3xTgAD	<168.1	<168.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
									TAU	8
	DHA-diet 3	N/A		Oral	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8
	DHA-diet 3	N/A		Oral	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									TAU	8
Riddell et al. (2007)	TO901317	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
	TO901317	30	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
	TO901317	50	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
									Fear conditioning	18

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Hemming, Selkoe, & Farris (2007)	captopril	2	g/l	Oral	U	3xTgAD	<168.1	<168.1	Amyloid beta 40	17.5
									Amyloid beta 42	17.5
	Losartan	0.6	g/l	Oral	U	3xTgAD	<168.1	<168.1	Amyloid beta 40	17.5
									Amyloid beta 42	17.5
	captopril	2	g/l	Oral	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	19
									Amyloid beta 42	19
	captopril	2	g/l	Oral	U	APP	>336 and <504.1	>336 and <504.1	Plaque area	8
Chen et al. (2007)	A beta 1-42	N/A		SubCut	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	34
	A beta 1-42	N/A		SubCut	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	42
Matsuoka et al. (2007)	NAP	0.5	µg	INasal	U	3xTgAD	>168 and <336.1	>336 and <504.1	Amyloid beta 40	22
									Amyloid beta 42	22
									TAU	22
Nikolic et al. (2007)	A beta 1-42	200	µg	SubCut	B	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	18
									Amyloid beta 42	18
									Plaque area	18
Rockenstein et al. (2007b)	Lithium	20	mg/kg/day	Iperitoneal	U	APP	<168.1	>168 and <336.1	Acquisition	12
									Amyloid beta 42	12
									Plaque area	12
									Probe	12
									TAU	12
Becker, Lavie, & Solomon (2007)	EFRH	N/A		Iperitoneal	B	APP	<168.1	>336 and <504.1	Cellular infiltrates	24
									Neurodegeneration	24
Billings et al. (2007)	Learning	N/A		N/A	B	3xTgAD	<168.1	>168 and <336.1	Amyloid beta 40	15

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	15
									Plaque area	15
									TAU	15
	Learning	N/A		N/A	B	3xTgAD	<168.1	>504	Acquisition	18
	Learning	N/A		N/A	B	3xTgAD	<168.1	>504	Acquisition	18
	Learning	N/A		N/A	B	3xTgAD	<168.1	>336 and <504.1	Acquisition	18
	Learning	N/A		N/A	B	3xTgAD	<168.1	>336 and <504.1	Probe	18
	Learning	N/A		N/A	B	3xTgAD	<168.1	>336 and <504.1	Probe	14
	Learning	N/A		N/A	B	PS1	<168.1	>504	Acquisition	18
	Learning	N/A		N/A	B	PS1	<168.1	>336 and <504.1	Probe	18
	Learning	N/A		N/A	B	3xTgAD	<168.1	>504	Acquisition	21
	Learning	N/A		N/A	B	3xTgAD	<168.1	>336 and <504.1	Acquisition	11
	Learning	N/A		N/A	B	3xTgAD	<168.1	>504	Acquisition	18
	Learning	N/A		N/A	B	3xTgAD	<168.1	>336 and <504.1	Probe	21
	Learning	N/A		N/A	B	3xTgAD	<168.1	>336 and <504.1	Probe	11
Best et al. (2007)	MRK-560	3	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	44
									Amyloid beta 42	44
									Cellular infiltrates	6
									Plaque area	24
	MRK-560	3	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	6
Liu et al. (2007)	nicotine	195	ug/day	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	10
									Amyloid beta 42	10
									Plaque area	10

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Li et al. (2006)	Simvastatin	50	mg/kg/day	Oral	F	APP	>168 and <336.1	>336 and <504.1	Acquisition	40
									Amyloid beta 40	40
									Amyloid beta 42	40
									Plaque area	40
									Probe	40
									T/Y maze	40
Wolf et al. (2006)	Exercise	N/A		N/A	F	APP	<168.1	>168 and <336.1	Acquisition	10
									Probe	10
								>336 and <504.1	Neurodegeneration	9
									Plaque area	10
	Environmental Enrichment	N/A		N/A	F	APP	<168.1	>168 and <336.1	Acquisition	9
									Probe	9
								>336 and <504.1	Neurodegeneration	9
									Plaque area	9
Chauhan (2006)	Garlic extract	20	mg/kg	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	6.667
									Amyloid beta 42	6.667
									Plaque area	6.667
									TAU	6.667
	SAC	20	mg/kg	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	6.667
									Amyloid beta 42	6.667
									Plaque area	6.667
									TAU	6.667
	DADS	20	mg/kg	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	6.667
									Amyloid beta 42	6.667

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	6.667
									TAU	6.667
Hartman et al. (2006)	Pomegranate juice	5	ml/day	Oral	U	APP	<168.1	>168 and <336.1	Acquisition	41
								>336 and <504.1	Amyloid beta 40	38
									Amyloid beta 42	40
									Plaque area	47
									Probe	41
Wang et al. (2006)	Cabernet Sauvignon	N/A		Oral	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	12
									Amyloid beta 42	12
Holcomb et al. (2006)	Bacopa Monniera	40	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	15
									Amyloid beta 42	15
	Bacopa Monniera	160	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
	Bacopa Monniera	40	mg/kg/day	Oral	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	14.5
									Amyloid beta 42	14.5
									T/Y maze	14.5
	Bacopa Monniera	160	mg/kg/day	Oral	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	12.5
									Amyloid beta 42	12.5
									T/Y maze	12.5
Oksman et al. (2006)	DHA	N/A		Oral	M	APPPS	<168.1	>168 and <336.1	Acquisition	21.66
									Amyloid beta 40	21.67
									Amyloid beta 42	21.67
	Typical Western Diet	N/A		Oral	M	APPPS	<168.1	>168 and <336.1	Acquisition	21.66
									Amyloid beta 40	21.67

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	21.67
	Lipid Neutral Diet	N/A		Oral	M	APPPS	<168.1	>168 and <336.1	Acquisition	21.66
									Amyloid beta 40	21.67
									Amyloid beta 42	21.67
	Fish oil-based diet	N/A		Oral	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 42	10.5
									Cellular infiltrates	10.5
	Corn oil	N/A		Oral	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 42	10.5
									Cellular infiltrates	10.5
Carro et al. (2006)	Insulin-like Growth factor 1	50	micro g/day	SubCut	U	APPPS	>168 and <336.1	>336 and <504.1	Acquisition	24
									Amyloid beta 40	10
									Amyloid beta 42	10
									Cellular infiltrates	24
									Neurodegeneration	24
									Plaque area	10
Ethell et al. (2006)	T cells	N/A		Ivenous	U	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40	11
									Amyloid beta 42	11
									Cellular infiltrates	11
									RAWM	11
	T cells	N/A		Ivenous	U	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40	11
									Amyloid beta 42	11
									Cellular infiltrates	13
	T cells	N/A		Ivenous	U	APPPS	>168 and <336.1	>168 and <336.1	RAWM	15
									T/Y maze	15
Mori et al. (2006)	Arundic Acid	10	mg/kg	Oral	M	APP	>168 and <336.1	>504	Amyloid beta 40	29

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	29
									Cellular infiltrates	29
									Plaque area	29
Okura et al. (2006)	A beta 1-42	N/A		intramuscular	U	APP	<168.1	>168 and <336.1	Plaque area	20
	A beta 1-42	N/A		intramuscular	U	APP	<168.1	>168 and <336.1	Plaque area	20
	A beta 1-42	N/A		intramuscular	U	APP	<168.1	>336 and <504.1	Plaque area	24
	A beta 1-42	N/A		intramuscular	U	APP	<168.1	>168 and <336.1	Plaque area	20
	A beta 1-42	N/A		intramuscular	U	APP	<168.1	>336 and <504.1	Plaque area	24
Wilcock et al. (2006)	Antibody 2h6	10	mg/kg/week	Iperitoneal	U	APP	>504	>504	Cellular infiltrates	7.5
									Plaque area	7.5
									RAWM	7.5
	Antibody 2h6 (deglycosylated)	10	mg/kg/week	Iperitoneal	U	APP	>504	>504	Cellular infiltrates	8.5
									Plaque area	8.5
									RAWM	8.5
Maier et al. (2006)	A beta 1-15	N/A		INasal	U	APP	<168.1	<168.1	Acquisition	13
									Amyloid beta 40	13
									Amyloid beta 42	13
									Plaque area	13
									Probe	13
Caccamo et al. (2006)	AF267B	2	mg/kg/day	Iperitoneal	U	3xTgAD	<168.1	>168 and <336.1	Acquisition	20
									Amyloid beta 40	20
									Amyloid beta 42	20
									Plaque area	20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Probe	20
									TAU	20
	Dicyclomine	8	mg/kg/day	Iperitoneal	U	3xTgAD	<168.1	>168 and <336.1	Acquisition	14
									Amyloid beta 40	14
									Amyloid beta 42	14
									Plaque area	14
									Probe	14
									TAU	14
Unger et al. (2006)	Galantamine	2	mg/kg/day	SubCut	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	5.333
									Amyloid beta 42	5.333
									Neurodegeneration	6.667
	Memantine	10	mg/kg/day	SubCut	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	5.333
									Amyloid beta 42	5.333
									Neurodegeneration	6.667
	nicotine	0.42	mg/kg	SubCut	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6.667
									Amyloid beta 42	6.667
									Neurodegeneration	6.667
Van Dam & De Deyn (2006)	Galantamine	2.6	mg/kg/day	SubCut	M	APP	<168.1	<168.1	Acquisition	13.5
									Probe	13.5
	Galantamine	7.2	mg/kg/day	SubCut	M	APP	<168.1	<168.1	Acquisition	13.5
									Probe	13.5
	Memantine	7.2	mg/kg/day	SubCut	M	APP	<168.1	<168.1	Acquisition	13.5
									Probe	13.5
	Memantine	14.4	mg/kg/day	SubCut	M	APP	<168.1	<168.1	Acquisition	12.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Probe	12.5
Asai et al. (2006)	KMI-429	10	nM	iHippocampus	M	APP	<168.1	<168.1	Amyloid beta 40	5.333
									Amyloid beta 42	5.333
	KMI-358	10	nM	iHippocampus	M	APP	<168.1	<168.1	Amyloid beta 40	5.333
									Amyloid beta 42	5.333
	N-benzyloxycarbonyl-valine-leucine-leucinal	2.5	nmol	iHippocampus	M	APP	<168.1	<168.1	Amyloid beta 40	5.333
									Amyloid beta 42	5.333
Nakashima et al. (2005)	Lithium	2	LICL/kg	Oral	U	Tau	<168.1	<168.1	TAU	7.5
	Lithium	2	LICL/kg	Oral	U	Tau	<168.1	>168 and <336.1	TAU	6
	Lithium	2	LICL/kg	Oral	U	Tau	<168.1	>168 and <336.1	TAU	6
Tamura et al. (2005)	Antibody Fc fragment	N/A		Iperitoneal	U	APP	>336 and <504.1	>504	Amyloid beta 40	9
									Amyloid beta 42	9
	Antibody Fc fragment	N/A		intracranial	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
	Antibody Fc fragment	N/A		intracranial	U	APP	>504	>504	Amyloid beta 40	6.667
									Amyloid beta 42	6.667
	Antibody p-F(ab')2	N/A		Iperitoneal	U	APP	>336 and <504.1	>504	Amyloid beta 40	9
									Amyloid beta 42	9
	Antibody p-F(ab')2	N/A		intracranial	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	10.33
									Amyloid beta 42	10.33
	Antibody p-F(ab')2	N/A		intracranial	U	APP	>504	>504	Amyloid beta 40	7.667
									Amyloid beta 42	7.667
	Antibody anti-beta-13	N/A		Iperitoneal	U	APP	>336 and <504.1	>504	Amyloid beta 40	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	8
	Antibody anti-beta-13	N/A		intracranial	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	10.33
									Amyloid beta 42	10.33
	Antibody anti-beta-13	N/A		intracranial	U	APP	>504	>504	Amyloid beta 40	6.667
									Amyloid beta 42	6.667
Zurbriggen et al. (2005)	a beta 1-16	N/A		intramuscular	B	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	36
									Amyloid beta 42	36
									Plaque area	36
Buttini et al. (2005)	A beta 1-42	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	20
									Neurodegeneration	14.67
									Plaque area	20
	Antibody 12B4	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	24
									Neurodegeneration	24
									Plaque area	24
	Antibody 3d6	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	24
									Neurodegeneration	24
									Plaque area	24
	A beta 15-24	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	20
									Neurodegeneration	20
									Plaque area	20
	A beta 3-9	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	20
									Neurodegeneration	14.67
									Plaque area	20
	a beta 1-5	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 42	20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Neurodegeneration	14.67
									Plaque area	20
Comery et al. (2005)	DAPT	100	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	16
									Amyloid beta 42	16
									Fear conditioning	12
	DAPT	100	mg/kg/day	Oral	M	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	16
	DAPT	100	mg/kg/day	Oral	M	APP	>336 and <504.1	>336 and <504.1	Fear conditioning	16
	DAPT	100	mg/kg/day	Oral	M	APP	<168.1	<168.1	Fear conditioning	16
	Rolipram	0.1	mg/kg/day	Iperitoneal	M	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	16
Dong et al. (2005)	Donepezil	0.1	mg/kg/day	SubCut	B	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	7.667
	Donepezil	0.3	mg/kg/day	SubCut	B	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	7.667
	Donepezil	1	mg/kg/day	SubCut	B	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	7.667
									Plaque area	10
	Physostigmine	0.03	mg/kg/day	SubCut	B	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	6.667
	Physostigmine	0.1	mg/kg/day	SubCut	B	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	6.667
	Physostigmine	0.3	mg/kg/day	SubCut	B	APP	>168 and <336.1	>168 and <336.1	Fear conditioning	6.667
									Plaque area	10
Frenkel et al. (2005)	A beta 1-40	N/A		Iperitoneal	U	APP	>336 and <504.1	<168.1	Cellular infiltrates	15
Calon et al. (2005)	DHA	N/A		Oral	B	APP	>336 and <504.1	>504	Neurodegeneration	7.5
	DHA-diet 1	N/A		Oral	B	APP	>336 and <504.1	>504	Neurodegeneration	7.5
Hartman et al. (2005)	Antibody 10d5	N/A		Iperitoneal	B	APP	>336 and <504.1	>336 and <504.1	Acquisition	23
								>504	Amyloid beta 40	18
									Amyloid beta 42	18

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	18
Dam et al. (2005)	Donepezil	0.3	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	12.87 12.88
	Donepezil	0.6	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	12.87 12.88
	Galantamine	1.25	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	15.87 15.88
	Galantamine	2.5	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	15.87 15.88
	Rivastigmine	0.5	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	16.87 14.21
	Rivastigmine	1	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	12.87 12.88
	Memantine	2	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	14.87 13.88
	Memantine	10	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	Acquisition Probe	11.87 11.88
Noble et al. (2005)	Lithium	10	microlitres per gram	Iperitoneal	B	Tau	>168 and <336.1	>168 and <336.1	Neurodegeneration TAU	12 10.67
	AR-A014418	10	microlitres per gram	Iperitoneal	B	Tau	>168 and <336.1	>168 and <336.1	TAU	20
Adlard et al. (2005)	Exercise	N/A		N/A	F	APP	<168.1	>168 and <336.1	Acquisition Plaque area	10 10
Quinn et al. (2005)	Melatonin	16	ug/mL	Oral	F	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	14

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	14
									Plaque area	14
Lim et al. (2005)	DHA	0.02	w/w	Oral	B	APP	>336 and <504.1	>504	Amyloid beta 40	10
									Amyloid beta 42	10
	DHA	0.6	w/w	Oral	B	APP	>336 and <504.1	>504	Amyloid beta 40	10
									Amyloid beta 42	10
Lazarov et al. (2005)	Environmental Enrichment	N/A		N/A	U	APPPS	<168.1	<168.1	Amyloid beta 40	13
									Amyloid beta 42	13
	Environmental Enrichment	N/A		N/A	U	APPPS	<168.1	<168.1	Plaque area	16
De Rosa et al. (2005)	NGF	N/A		INasal	U	other	not known	not known	NORT	42
	NGF	N/A		INasal	U	other	not known	not known	NORT	36
Billings et al. (2005)	Antibody 1560	N/A		IVentricular	B	3xTgAD	<168.1	<168.1	Acquisition	8
									Fear conditioning	8
									Probe	8
	Antibody 1560	N/A		IVentricular	B	3xTgAD	<168.1	<168.1	Acquisition	11
									Fear conditioning	11
									Probe	11
	Learning	N/A		N/A	B	PS1	<168.1	>168 and <336.1	Probe	24
	Learning	N/A		N/A	B	3xTgAD	<168.1	>168 and <336.1	Probe	30
	Learning	N/A		N/A	B	3xTgAD	<168.1	>168 and <336.1	Probe	29
Yang et al. (2005)	Curcumin	500	ppm	Oral	U	APP	>336 and <504.1	>504	Plaque area	10
Anderson et al. (2005)	BMS-289948 (also known as SIB-3399)	5	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	BMS-289948 (also known as SIB-3399)	25	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-289948 (also known as SIB-3399)	50	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-289948 (also known as SIB-3399)	100	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-289948 (also known as SIB-3399)	175	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-289948 (also known as SIB-3399)	100	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-299897 (also known as SIB-3520)	1.5	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-299897 (also known as SIB-3520)	5	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-299897 (also known as SIB-3520)	15	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-299897 (also known as SIB-3520)	50	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-299897 (also known as SIB-3520)	150	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	9.6
	BMS-299897 (also known as SIB-3520)	100	mg/kg/day	Oral	U	APP	not known	not known	Amyloid beta 40	16
Bowers et al. (2005)	A beta 1-42	N/A		SubCut	U	APP	<168.1	>168 and <336.1	Plaque area	7
Wang et al. (2005)	Caloric restriction	N/A		Oral	F	APP	<168.1	>168 and <336.1	Amyloid beta 40 Amyloid beta 42	10 10
Rockenstein et al. (2005)	Cerebrolysin	5	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	12
	Cerebrolysin	5	mg/kg	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	12
Zhang et al. (2005)	paclitaxel	25	mg/m squared	Iperitoneal	U	Tau	>168 and <336.1	>168 and <336.1	Neurodegeneration	4.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									TAU	18
	paclitaxel	10	mg/m squared	Iperitoneal	U	Tau	>168 and <336.1	>168 and <336.1	Neurodegeneration	4.5
									TAU	18
Jensen et al. (2005)	A beta 1-42	N/A		SubCut	U	APPPS	<168.1	>336 and <504.1	Acquisition	8
									Plaque area	8
									Probe	8
									RAWM	8
									T/Y maze	8
Chauhan, Siegel, & Lichtor (2004)	Antibody Amy-33	N/A		intraventriclular	U	APP	<168.1	<168.1	Plaque area	10
	Antibody Amy-33	N/A		intraventriclular	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	10
Arendash et al. (2004)	Environmental Enrichment	N/A		N/A	U	APP	>336 and <504.1	>504	Acquisition	9
									Plaque area	9
									Probe	9
Schultz et al. (2004)	Antibody 16E6	N/A		Ivenous	U	APP	<168.1	<168.1	Amyloid beta 42	8
	Antibody 16G1	N/A		Ivenous	U	APP	<168.1	<168.1	Amyloid beta 42	8
Herber et al. (2004)	LPS	4	ug/ul	iHippocampus	U	APP	>336 and <504.1	>336 and <504.1	Plaque area	6
	LPS	10	ug/ul	iHippocampus	U	APP	>336 and <504.1	>336 and <504.1	Plaque area	6
	LPS	4	ug/ul	iHippocampus	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates	8
									Plaque area	8
Lee et al. (2004)	DP-109	5	mg/kg	Oral	F	APP	>504	>504	Amyloid beta 40	28
									Amyloid beta 42	28
									Plaque area	28

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Minkeviciene, Banerjee, & Tanila (2004)	Memantine	30	mg/kg/day	Oral	M	APPPS	>168 and <336.1	>168 and <336.1	Acquisition	45
Bussiere et al. (2004)	Antibody 10d5	10	mg/kg/week	Iperitoneal	U	APP	>336 and <504.1	>504	Plaque area	14.67
	Antibody 12B4	10	mg/kg/week	Iperitoneal	U	APP	>336 and <504.1	>504	Plaque area	14.67
	Antibody 12A11	10	mg/kg/week	Iperitoneal	U	APP	>336 and <504.1	>504	Plaque area	17
Seabrook et al. (2004)	A beta 40/42	N/A		Iperitoneal	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40 Amyloid beta 42	6 6
	A beta 40/42	N/A		Iperitoneal	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40 Amyloid beta 42	6 6
Oddo et al. (2004)	Antibody 1560	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	6 6
	Antibody 1560	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	6 6
	Antibody 1560	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	12 9
	Antibody 1560	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	6 6
	Antibody HT7	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	6 6
	Antibody 4G8	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	6 6
	Antibody 1560	N/A		iHippocampus	B	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area TAU	6 6

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Antibody 1560	N/A		iHippocampus	B	3xTgAD	<168.1	>168 and <336.1	Plaque area TAU	10 10
Etcheberrigaray et al. (2004)	bryostatin 1	1	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 40	8
	bryostatin 1	40	ug/kg	Iperitoneal	B	APPPS	<168.1	>168 and <336.1	Amyloid beta 40 Amyloid beta 42	30 30
Sigurdsson et al. (2004)	A beta 1-30	N/A		SubCut	U	APP	>168 and <336.1	>504	Plaque area RAWM	36 32
	A beta 1-30	N/A		SubCut	U	APP	>168 and <336.1	>504	RAWM	14
Wilcock et al. (2004)	Antibody 2286	10	mg/kg	Iperitoneal	U	APP	>504	>504	Cellular infiltrates Plaque area T/Y maze	7 5 7
Nakashima et al. (2004)	alpha-tocopherol	160	IU/kg	Oral	U	Tau	<168.1	<168.1	TAU	4.5
	alpha-tocopherol	1500	IU/kg	Oral	U	Tau	<168.1	<168.1	TAU	4.5
	alpha-tocopherol	160	IU/kg	Oral	U	Tau	<168.1	>168 and <336.1	TAU	4.5
	alpha-tocopherol	1500	IU/kg	Oral	U	Tau	<168.1	>168 and <336.1	TAU	4.5
Chang et al. (2004)	OMOO-3 DR9	8	mg/kg/day	Iperitoneal	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	12
Su et al. (2004)	Lithium	300	mg/kg	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	20
	Lithium	600	mg/kg	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	15
	Lithium	300	mg/kg	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	15
	Lithium	2.4	mg/kg	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 42 Plaque area	15 20
	Valproic acid	400	mg/kg	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	15
	Lithium	N/A			U	Tau	>168 and <336.1	>168 and <336.1	Amyloid beta 40	20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
George et al. (2004)	High Cholesterol	N/A		Oral	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	15
Hellstrom-Lindahl et al. (2004)	nicotine	0.42	mg/kg	SubCut	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	10
									Amyloid beta 42	11
	nicotine	200	ug/mL	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	9
									Amyloid beta 42	9
									Plaque area	9
Bergamaschini et al. (2004)	Enoxaparin (a Heparin)	60	µg	Iperitoneal	M	APP	<168.1	>168 and <336.1	Amyloid beta 40	14
									Plaque area	12
Wong et al. (2004)	LY-411575	1	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	8.75
									Amyloid beta 42	8.75
	LY-411575	10	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	8.75
									Amyloid beta 42	8.75
	LY-D	1	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	8.75
									Amyloid beta 42	8.75
	LY-D	10	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	8.75
									Amyloid beta 42	8.75
Iwata et al. (2004)	Neprilysin	0.6	µl	iHippocampus	U	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
	Neprilysin	0.6	µl	iHippocampus	U	APP	>504	>504	Plaque area	12
Sung et al. (2003)	Vitamin E	2	I.U./g	Oral	B	APP	<168.1	>336 and <504.1	Amyloid beta 40	20
									Amyloid beta 42	20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	20
	Vitamin E	2	I.U./g	Oral	B	APP	>336 and <504.1	>504	Amyloid beta 40	20
									Amyloid beta 42	20
									Plaque area	20
Zhang et al. (2003)	A beta 1-42	N/A		Oral	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	10.33
									Amyloid beta 40	10.33
									Amyloid beta 42	10.33
									Plaque area	10.33
									Probe	9.333
	A beta 1-42	N/A		INasal	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	10.33
									Amyloid beta 40	10.33
									Amyloid beta 42	10.33
									Plaque area	10.33
									Probe	10.33
	A beta 1-42	N/A		intramuscular	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	10.33
									Amyloid beta 40	10.33
									Amyloid beta 42	10.33
									Plaque area	10.33
									Probe	10.33
	A beta 1-42	N/A		Oral	U	APP	<168.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12
									Probe	12
	A beta 1-42	N/A		INasal	U	APP	<168.1	>336 and <504.1	Amyloid beta 40	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	12
									Plaque area	12
				intramuscular	U	APP	<168.1	>336 and <504.1	Probe	12
	A beta 1-42	N/A		INasal	U	APP	<168.1	>336 and <504.1	Probe	11
				intramuscular	U	APP	<168.1	>336 and <504.1	Amyloid beta 40	11
									Amyloid beta 42	11
									Plaque area	11
	A beta 1-42	N/A		intramuscular	U	APP	<168.1	>336 and <504.1	Acquisition	11
	A beta 1-42	N/A		INasal	U	APP	<168.1	>336 and <504.1	Acquisition	12
	A beta 1-42	N/A		Oral	U	APP	<168.1	>336 and <504.1	Acquisition	12
	A beta 1-42	N/A		Oral	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	9.33
									Amyloid beta 40	9.333
									Amyloid beta 42	9.333
									Plaque area	9.333
									Probe	10.33
	A beta 1-42	N/A		INasal	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	10.33
									Amyloid beta 40	10.33
									Amyloid beta 42	10.33
									Plaque area	10.33
									Probe	10.33
	A beta 1-42	N/A		intramuscular	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	10.33
									Amyloid beta 40	10.33
									Amyloid beta 42	10.33
									Plaque area	10.33

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Probe	10.33
Ryder et al. (2003)	Lithium	200	mg/kg	Oral	U	APP	<168.1	<168.1	Amyloid beta 42	16
	Roscovitine	30	nM	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 42	20
	Roscovitine	50	nM	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 42	20
Hasegawa et al. (2003)	A beta 1-42	N/A		Unknown	U	APP	<168.1	<168.1	Acquisition	21
								>168 and <336.1	Plaque area	21
Lombardo et al. (2003)	Antibody 10d5	N/A		icerebral	U	APP	>504	>504	Plaque area	16
	Antibody 10d5	N/A		icerebral	U	APP	>504	>504	Plaque area	16
Bayer et al. (2003)	Copper	0.25	grams/liter	Oral	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	11
									Amyloid beta 42	11
									Plaque area	11
	Copper	0.25	grams/liter	Oral	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	15
Stackman et al. (2003)	Gingko Biloba	70	mg/kg/day	Oral	F	APP	>168 and <336.1	>336 and <504.1	Acquisition	16
									Amyloid beta 40	16
									Amyloid beta 42	16
									Plaque area	16
									Probe	16
Rockenstein et al. (2003)	Cerebrolysin	5	ml/kg	Iperitoneal	U	APP	<168.1	>168 and <336.1	Acquisition	24
									Neurodegeneration	24
									Plaque area	24
	Cerebrolysin	5	ml/kg	Iperitoneal	U	APP	<168.1	>168 and <336.1	Acquisition	24
									Neurodegeneration	24

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	24
Zhou et al. (2003)	Y-27632	2	mg/kg/day	IVentricular	U	APP	<168.1	<168.1	Amyloid beta 42	20
Lemere et al. (2003)	A beta 40/42	200	ug/week	multiple	B	APPPS	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	10.5
									Plaque area	10
Yan et al. (2003)	Ibuprofen	62.5	mg/kg/day	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
									Cellular infiltrates	7
									Plaque area	7
	Pioglitazone	20	mg/kg/day	Oral	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	6.5
									Amyloid beta 42	6.5
									Cellular infiltrates	6
									Plaque area	6
Park et al. (2003)	Lovastatin	100	mg/kg/day	Oral	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	14
									Amyloid beta 42	14
									Plaque area	14
	Lovastatin	100	mg/kg/day	Oral	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	14
									Amyloid beta 42	14
									Plaque area	14
Joseph et al. (2003)	Blueberry supplementation	20	g/kg/day	Oral	U	APPPS	<168.1	>168 and <336.1	T/Y maze	6
Austin et al. (2003)	A beta 1-42	N/A		SubCut	B	APPPS	>336 and <504.1	>504	RAWM	26
Wilcock et al. (2003)	Antibody anti-beta 1-16	N/A		multiple	U	APP	>336 and <504.1	>336 and <504.1	Cellular infiltrates	13
									Plaque area	13
Quinn et al. (2003)	Indomethacin	2.24	mg/kg/day	Oral	F	APP	>168 and <336.1	>504	Plaque area	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Indomethacin	2.24	mg/kg/day	Oral	F	APP	>168 and <336.1	>336 and <504.1	Plaque area	5.333
	LPS	25	mg/kg	Iperitoneal	F	APP	>336 and <504.1	>336 and <504.1	Plaque area	5.333
	LPS	25	mg/kg	Iperitoneal	F	APP	>336 and <504.1	>336 and <504.1	Plaque area	5.333
Marr et al. (2003)	Neprilysin	15000000	TU	icerebral	U	APP	>336 and <504.1	>336 and <504.1	Plaque area	25
Bard et al. (2003)	A beta 15-24	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	37.75
	Antibody 6C6	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Neurodegeneration	35.67
	a beta 1-5	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	35.75
	A beta 5-11	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	38.75
	A beta 3-9	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	42.75
	Antibody 2C1	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Neurodegeneration	31.67
	Antibody 3A3	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Neurodegeneration	34.67
	Antibody 10d5	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Neurodegeneration	36.67
	Antibody 12B4	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Neurodegeneration	34.67
	Antibody 12A11	10	mg/kg/week	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Neurodegeneration	39.67
Matsuoka et al. (2003)	GM1 ganglioside	15	mg/kg/body	IVentricular	B	APPPS	<168.1	<168.1	Amyloid beta 40 Amyloid beta 42	11 11
	GM1 ganglioside	15	mg/kg/body weight/2 days	Iperitoneal	B	APPPS	<168.1	<168.1	Amyloid beta 40 Amyloid beta 42	11 11
	Gelsolin	N/A		Iperitoneal	B	APPPS	<168.1	<168.1	Amyloid beta 40	14.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	14.5
									Plaque area	10
Town et al. (2002)	A beta 1-42	N/A		Iperitoneal	B	APP	<168.1	>504	Plaque area	8
Capsoni, Giannotta, & Cattaneo (2002)	Galantamine	3.5	mg/kg/day	Iperitoneal	U	other	<168.1	>168 and <336.1	Plaque area	6.25
	Galantamine	3.5	mg/kg/day	Iperitoneal	U	other	<168.1	<168.1	Plaque area	6.25
	NGF	48	ul	Iperitoneal	U	other	<168.1	>168 and <336.1	Plaque area	5.25
	NGF	48	ul	Iperitoneal	U	other	<168.1	<168.1	Plaque area	5.25
Rockenstein et al. (2002)	Cerebrolysin	4	mg/kg	Iperitoneal	U	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12
Petanceska et al. (2002)	atorvastatin	N/A		Oral	B	APPPS	<168.1	<168.1	Amyloid beta 40	16
									Amyloid beta 42	16
									Plaque area	16
Kotilinek et al. (2002)	Antibody BAM-10	N/A		Iperitoneal	B	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	37
									Amyloid beta 42	37
	Antibody BAM-10	N/A		Iperitoneal	B	APP	>168 and <336.1	>168 and <336.1	Probe	27
Chauhan & Siegel (2002)	Antibody Amy-33	N/A		intraventriclular	M	APP	>168 and <336.1	>168 and <336.1	Cellular infiltrates	10
									Plaque area	10
Nordberg et al. (2002)	nicotine	30	mg/kg	Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
Permanne et al. (2002)	iA-beta-5	N/A	mg/week	Iperitoneal	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	22
									Amyloid beta 42	22

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	22
	iA-beta-5	N/A	mg/week	intraventriclular	U	APPPS	>168 and <336.1	>168 and <336.1	Neurodegeneration	9
									Plaque area	9
	iA-beta-5	N/A	mg/week	Iperitoneal	U	APPPS	>168 and <336.1	>168 and <336.1	Neurodegeneration	11
									Plaque area	11
Dodart et al. (2002)	Antibody m266	200		Iperitoneal	M	APP	>504	>504	NORT	16
									Plaque area	16
	Antibody m266	10		Iperitoneal	M	APP	>168 and <336.1	>168 and <336.1	NORT	10.67
	Antibody m266	50		Iperitoneal	M	APP	>168 and <336.1	>168 and <336.1	NORT	10.67
	Antibody m266	250		Iperitoneal	M	APP	>168 and <336.1	>168 and <336.1	NORT	10.67
	Antibody m266	360		Iperitoneal	M	APP	>168 and <336.1	>168 and <336.1	NORT	16
Jantzen et al. (2002)	Ibuprofen	62.5	mg/kg/day	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates	9.333
									Plaque area	9.333
	celecoxib	30	mg/kg/day	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates	9.333
									Plaque area	9.333
	NCX-2216	62.5	mg/kg/day	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates	9.333
									Plaque area	9.333
	NCX-2216	62.5	mg/kg/day	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates	14
Liu et al. (2002)	Metrifonate	100	mg/kg/day	Oral	M	APPPS	>168 and <336.1	>336 and <504.1	Acquisition	56
									Amyloid beta 40	36
									Amyloid beta 42	36
									Plaque area	36
Vehmas et al. (2001)	A beta 1-42	100	mg	Iperitoneal	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	7

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	7
									Plaque area	7
	A beta 1-42	100	mg	Iperitoneal	U	APPPS	<168.1	>168 and <336.1	Plaque area	10.5
Arendash et al. (2001)	A beta 1-42	N/A		SubCut	U	APPPS	>168 and <336.1	>336 and <504.1	Plaque area	8
									RAWM	8
									T/Y maze	20
Das et al. (2001)	A beta 1-42	N/A		Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
	A beta 1-42	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
	A beta 1-42	N/A		Iperitoneal	U	APP	>504	>504	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
Refolo et al. (2001)	BM15-766	250	mg/kg/day	Oral	B	APPPS	<168.1	<168.1	Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	15
Lim et al. (2001)	Curcumin	160	ppm	Oral	B	APP	>168 and <336.1	>336 and <504.1	Cellular infiltrates	17
									Plaque area	17
Sigurdsson et al. (2001)	A beta 1-30	N/A		SubCut	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
DeMattos et al. (2001)	Antibody m266	N/A		Iperitoneal	U	APP	<168.1	>168 and <336.1	Amyloid beta 42	28
									Plaque area	27

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Janus et al. (2000)	A beta 1-42	N/A		Iperitoneal	U	APP	<168.1	<168.1	Acquisition	16
								>168 and <336.1	Plaque area	16
Morgan et al. (2000)	A beta 1-42	N/A		SubCut	B	APP	>168 and <336.1	>336 and <504.1	Plaque area	5
									RAWM	5
	A beta 1-42	N/A		SubCut	B	APPPS	>168 and <336.1	>336 and <504.1	Plaque area	9
									RAWM	9
Weiner et al. (2000)	A beta 1-40	10	ug/week	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 42	6
									Plaque area	13.5
	A beta 1-40	10	ug/week	Oral	U	APP	<168.1	>168 and <336.1	Plaque area	13.5
	A beta 1-40	5	ug/week	INasal	U	APP	<168.1	>168 and <336.1	Amyloid beta 42	5
									Plaque area	11.5
	A beta 1-40	25	ug/week	INasal	U	APP	<168.1	>168 and <336.1	Amyloid beta 42	6
									Plaque area	13.5
	A beta 1-40	100	ug/week	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 42	6
Lim et al. (2000)	Ibuprofen	56	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Cellular infiltrates	14
									Neurodegeneration	15
									Plaque area	12
Schenk et al. (1999)	A beta 1-42	N/A		Iperitoneal	F	APP	<168.1	>336 and <504.1	Plaque area	14
	A beta 1-42	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Plaque area	18
	A beta 1-42	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Plaque area	19
	SAP protein	N/A		Iperitoneal	F	APP	<168.1	>336 and <504.1	Plaque area	9
Asami-Odaka et al. (2005)	Antibody BC05	0.95	mg/kg/week	Iperitoneal	M	APP	<168.1	>168 and <336.1	Amyloid beta 40	19
									Amyloid beta 42	19

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	19
Backer et al. (2008)	CNI-1493	8	mg/kg/day	Iperitoneal	M	APP	<168.1	<168.1	NORT	25
									Plaque area	9
Chauhan (2003)	Garlic extract	40	mg/kg/day	Oral	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	10
									Amyloid beta 42	10
Cherny et al. (2001)	Clioquinol	30	mg/kg/day	Oral	B	APP	>504	>504	Plaque area	27
Czirr et al. (2007)	LY-411575	10	mg/kg/day	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	9
	LY-411575	10	mg/kg/day	Oral	U	APPPS	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
Gong et al. (2004)	Rolipram	0.03	mg/kg/day	SubCut	B	APPPS	<168.1	>168 and <336.1	Fear conditioning	24
									Probe	24
									RAWM	31
	Rolipram	0.03	mg/kg/day	SubCut	B	APPPS	<168.1	>168 and <336.1	Acquisition	24
									Amyloid beta 40	34
									Amyloid beta 42	20
	Rolipram	0.03	mg/kg/day	SubCut	B	APPPS	<168.1	<168.1	Fear conditioning	24
									RAWM	31
Hemming et al. (2007)	Neprilysin	4	µl	iHippocampus	U	APP	>504	>504	Cellular infiltrates	8
									Plaque area	8
Kim et al. (2007a)	Resveratrol	N/A	5 ug/ml	IVentricular	U	Tau	<168.1	<168.1	Fear conditioning	14
	Resveratrol	N/A	mg/week	IVentricular	U	Tau	<168.1	<168.1	Cellular infiltrates	5
									Neurodegeneration	5
Levites et al. (2006b)	Antibody scFv9	N/A		IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	7.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	7.5
	Antibody scFv9	N/A		IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
									Plaque area	9.333
	Antibody scFv42.2	N/A		IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	Antibody scFv42.2	N/A		IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
									Plaque area	9.333
	Antibody scFv40.1	N/A		IVentricular	U	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
									Plaque area	9.333
Abramowski et al. (2008)	LY-411575	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	12
	LY-411575	10	mg/kg/day	Oral	M	APP	<168.1	>168 and <336.1	Amyloid beta 40	40
									Amyloid beta 42	40
									Plaque area	38
	LY-411575	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	10
	LY-411575	10	mg/kg/day	Oral	F	APPPS	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	10
	LY-411575	3	mg/kg	Oral	F	APPPS	>336 and <504.1	>336 and <504.1	Amyloid beta 40	30
									Amyloid beta 42	30
Adlard et al. (2008)	Clioquinol	30	mg/kg/day	Oral	B	APPPS	>504	>504	Amyloid beta 40	9
									Amyloid beta 42	9

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Clioquinol	30	mg/kg/day	Oral	B	APPPS	>504	>504	Neurodegeneration	9
									TAU	9
	PBT2	30	mg/kg/day	Oral	F	APPPS	>168 and <336.1	>168 and <336.1	Acquisition	25
									Probe	16
	Clioquinol	30	mg/kg/day	Oral	F	APPPS	>168 and <336.1	>168 and <336.1	Acquisition	16
									Probe	16
	PBT2	10	mg/kg/day	Oral	M	APPPS	>336 and <504.1	>336 and <504.1	Acquisition	13
									Probe	13
	PBT2	30	mg/kg/day	Oral	B	APPPS	>168 and <336.1	>168 and <336.1	Amyloid beta 40	9
									Amyloid beta 42	9
									Neurodegeneration	9
	PBT2	30	mg/kg/day	Oral	B	APPPS	>168 and <336.1	>168 and <336.1	TAU	9
	PBT2	30	mg/kg/day	Oral	B	APPPS	>168 and <336.1	>168 and <336.1	TAU	12
	PBT2	30	mg/kg/day	Oral	B	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	18
									Amyloid beta 42	18
	PBT2	30	mg/kg/day	Oral	B	APP	>336 and <504.1	>336 and <504.1	Neurodegeneration	18
									TAU	18
	PBT2	30	mg/kg/day	Oral	F	APP	>336 and <504.1	>336 and <504.1	Plaque area	12
Ambree et al. (2006)	Environmental Enrichment	N/A		N/A	F	APP	<168.1	<168.1	Amyloid beta 40	18
									Amyloid beta 42	18
									Cellular infiltrates	18
									Plaque area	18
Arendash et al. (2006)	Caffeine	1.5	mg/day	Oral	B	APP	<168.1	>168 and <336.1	Acquisition	41
									Probe	41

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Caffeine	1.5	mg/day	Oral	B	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
Arendash et al. (2007)	High Fat diet	N/A		Oral	U	APPPS	<168.1	>168 and <336.1	Acquisition	17
									Amyloid beta 40	17
									Amyloid beta 42	17
									Probe	17
									T/Y maze	17
Asuni et al. (2006)	A beta 1-30	N/A		SubCut	B	APP	>168 and <336.1	>504	Amyloid beta 40	28
									Amyloid beta 42	28
									Plaque area	28
									RAWM	33
	A beta 1-30	N/A		SubCut	B	APP	>504	>504	Amyloid beta 40	18
									Amyloid beta 42	18
									Plaque area	18
									RAWM	19
Barten et al. (2005)	BMS-299897 (also known as SIB-3520)	N/A		Oral	M	APP	<168.1	<168.1	Amyloid beta 40	6
	BMS-299897 (also known as SIB-3520)	N/A		Oral	M	APP	<168.1	>168 and <336.1	Amyloid beta 40	6
	BMS-299897 (also known as SIB-3520)	N/A		Oral	M	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6
	BMS-299897 (also known as SIB-3520)	N/A		Oral	M	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6
	BMS-299897 (also known as SIB-3520)	N/A		Oral	M	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	6
Boado et al. (2007)	antibody (fusion)	20	pmol	icerebral	M	APPPS	>336 and <504.1	>336 and <504.1	Plaque area	6

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Brendza et al. (2005)	Antibody 10d5	N/A		ibrain	U	APP	>336 and <504.1	>336 and <504.1	Neurodegeneration	17
Butovsky et al. (2006)	Glatiramer acetate	N/A		SubCut	U	APPPS	>168 and <336.1	>168 and <336.1	Acquisition	13
									Plaque area	13
	Glatiramer acetate	N/A		SubCut	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates	13
									Neurodegeneration	13
Casadesus et al. (2006)	Leuprolide	7.5	mg/kg	intramuscular	F	APP	>504	>504	Plaque area	13
									T/Y maze	13
Chauhan, Siegel, & Feinstein (2004)	Pravastatin	0.5	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
	Pravastatin	1	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
	Pravastatin	5	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
	Pravastatin	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
	Lovastatin	0.5	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
	Lovastatin	1	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	5.625
	Lovastatin	5	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
	Lovastatin	10	mg/kg/day	Oral	M	APP	<168.1	<168.1	Amyloid beta 40	5.625
									Amyloid beta 42	5.625
									Plaque area	5.625
Chauhan & Siegel (2005)	Antibody 2H4 (anti A beta 1-10)	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
	Antibody 1E11(anti A beta 1-10)	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
	Antibody IgG2b (anti A-beta 1-40)	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
	Antibody anti-beta 3-6	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
	Antibody anti-beta-11	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
	Antibody anti-beta 1-28	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
	Antibody beta-CTF	10	ugl10ul/animal	intraventriclular	U	APP	<168.1	<168.1	Plaque area	5.833
Chauhan & Siegel (2007)	Antisense Gamma-site ODN	10	nM/wk	IVentricular	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6.25
									Amyloid beta 42	6.25
	Antisense Beta-site ODN	10	nM/wk	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6.25
									Amyloid beta 42	6.25
	Gamma-secretase site ODN	10	nM/wk	IVentricular	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6.25
									Amyloid beta 42	6.25

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Beta-secretase site ODN	10	nM/wk	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6.25
									Amyloid beta 42	6.25
Chen, Eckman, & Eckman (2006)	LY-411575	25	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	21.5
									Amyloid beta 42	21.5
	Ginsenoside Rg3	25	mg/kg	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	14.5
									Amyloid beta 42	14.5
	Ginsenoside Rg1	25	mg/kg	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	15.5
									Amyloid beta 42	15.5
	Ginsenoside Re	25	mg/kg	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	23.5
									Amyloid beta 42	23.5
Cracchiolo et al. (2007)	Environmental Enrichment	N/A		N/A	B	APPPS	<168.1	>168 and <336.1	Plaque area	8.667
									Probe	8.667
									RAWM	8.667
	Exercise	N/A		N/A	B	APPPS	<168.1	>168 and <336.1	Plaque area	7.667
									Probe	7.667
									RAWM	7.667
	impoverished housing	N/A		N/A	B	APPPS	<168.1	>168 and <336.1	Plaque area	10.67
									Probe	10.67
									RAWM	10.67
DaSilva et al. (2006)	A beta 1-42	N/A		SubCut	U	APP	<168.1	>168 and <336.1	Cellular infiltrates	18
									Plaque area	20
	A beta 1-42	N/A		SubCut	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	20
									Amyloid beta 42	20
Dickstein et al. (2006)	A beta 1-40	N/A		Ivenous	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	A beta 1-40	N/A		Ivenous	U	APP	<168.1	>168 and <336.1	Plaque area	12
Dineley et al. (2007)	FK506	10	mg/kg	Iperitoneal	B	APP	<168.1	<168.1	Amyloid beta 42	10
									Fear conditioning	20
Dvir et al. (2006)	Indomethacin	50	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	10.5
									Amyloid beta 42	10.5
	Indomethacin	16.66	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	17.5
									Amyloid beta 42	17.5
	DP-115	135	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	11.5
									Amyloid beta 42	11.5
	DP-115	45	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	17.5
									Amyloid beta 42	17.5
Engel et al. (2006)	Lithium	1.98	g/kg	Oral	U	Tau	>504	>504	TAU	8
Esposito et al. (2008)	A beta 2-6	N/A		Iperitoneal	U	APPPS	<168.1	>168 and <336.1	Plaque area	4.5
	A beta 2-6	N/A		Iperitoneal	U	APPPS	<168.1	>336 and <504.1	Plaque area	8
	A beta 1-7	N/A		Iperitoneal	U	APPPS	<168.1	>168 and <336.1	Plaque area	4.5
Fan et al. (2007)	Minocycline	5	mg/kg/day	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	18
									Amyloid beta 42	18
									Cellular infiltrates	10
Feng et al. (2004)	Melatonin	10	mg/kg	Oral	U	APP	<168.1	>168 and <336.1	Neurodegeneration	20
Feng et al. (2006)	Melatonin	10	mg/kg	Oral	B	APP	<168.1	>168 and <336.1	Neurodegeneration	10
Fenili et al. (2007)	Scyllo-inositol	25	mg/animal	Oral	U	APP	<168.1	>168 and <336.1	Amyloid beta 40	18
									Amyloid beta 42	18
									Plaque area	18

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Frenkel et al. (2008)	Protollin	1	ug/mouse	INasal	U	APP	>504	>504	Amyloid beta 40 Amyloid beta 42 Cellular infiltrates	9.5 9.5 13
	Glatiramer acetate	25	ug/mouse	INasal	U	APP	<168.1	>336 and <504.1	Cellular infiltrates	13.5
Garcia-Alloza et al. (2006)	Egb- 761	100	mg/kg	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	66
	Trolox	210	mg/kg/day	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	66
Garcia-Alloza et al. (2007b)	Antibody 10d5	N/A		Icortex	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	4.5
	Antibody 10d5	N/A		Icortex	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	4.5
	Antibody 10d5	N/A		Icortex	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates Plaque area	4.5 6
	Antibody 10d5	N/A		Icortex	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	6
	Interferon-gamma	N/A		Icortex	U	APPPS	>168 and <336.1	>168 and <336.1	Cellular infiltrates Plaque area	4.5 4.5
	Interferon-gamma	N/A		Icortex	U	APPPS	>168 and <336.1	>168 and <336.1	Plaque area	4.5
Halagappa et al. (2007)	Intermittent Fasting	0.5	restricted	Oral	B	3xTgAD	<168.1	>336 and <504.1	Amyloid beta 40 Amyloid beta 42 Probe TAU	19.5 19.5 24 19.5
	Intermittent Fasting	0.5	restricted	Oral	B	3xTgAD	<168.1	>168 and <336.1	Acquisition Probe	25.5 24
	Caloric restriction	0.4	resricted	Oral	B	3xTgAD	<168.1	>336 and <504.1	Amyloid beta 40 Amyloid beta 42 Probe	19.5 19.5 24

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									TAU	19.5
	Caloric restriction	0.4	resricted	Oral	B	3xTgAD	<168.1	>168 and <336.1	Acquisition	25.5
									Probe	24
	Intermittent Fasting	0.5	resricted	Oral	M	3xTgAD	<168.1	>336 and <504.1	Acquisition	10.5
	Intermittent Fasting	0.5	resricted	Oral	F	3xTgAD	<168.1	>336 and <504.1	Acquisition	9
	Caloric restriction	0.5	resricted	Oral	M	3xTgAD	<168.1	>336 and <504.1	Acquisition	10.5
	Caloric restriction	0.4	resricted	Oral	F	3xTgAD	<168.1	>336 and <504.1	Acquisition	9
Heneka et al. (2005)	Pioglitazone	62.5	mg/kg/day	Oral	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	9
									Amyloid beta 42	9
									Cellular infiltrates	9
									Plaque area	9
	Ibuprofen	40	mg/kg/day	Oral	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	9
									Amyloid beta 42	9
									Cellular infiltrates	9
									Plaque area	9
Hooijmans et al. (2007)	DHA	N/A		Oral	M	APPPS	<168.1	>336 and <504.1	Plaque area	12
	Typical Western Diet	N/A		Oral	M	APPPS	<168.1	>336 and <504.1	Plaque area	13
Hook, Kindy, & Hook (2008)	CA074Me	0.006	mg/kg/day	SubCut	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7
									Amyloid beta 42	12
									Plaque area	12
	E64d	0.006	mg/kg/day	SubCut	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	CA074Me	0.006	mg/kg/day	SubCut	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12
	E64d	0.006	mg/kg/day	SubCut	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12
Hussain et al. (2007)	GSK-188909	250	mg/kg/day	Oral	M	APPPS	<168.1	<168.1	Amyloid beta 40	29
									Amyloid beta 42	29
	GSK-188909	250	mg/kg/day	Oral	M	APPPS	<168.1	<168.1	Amyloid beta 40	27
									Amyloid beta 42	26
	GF120918	250	mg/kg/day	Oral	M	APPPS	<168.1	<168.1	Amyloid beta 40	30
									Amyloid beta 42	30
Hyde et al. (2006)	LY-411575	0.1	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	0.3	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	1	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	3	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	10	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	0.1	mg/kg/day	SubCut	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	0.3	mg/kg/day	SubCut	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	1	mg/kg/day	SubCut	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	3	mg/kg/day	SubCut	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	10	mg/kg/day	SubCut	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
	LY-411575	10	mg/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	LY-411575	10	mg/kg/day	Oral	B	APP	>504	>504	Amyloid beta 40	8
	LY-D	10	g/kg/day	Oral	B	APP	<168.1	<168.1	Amyloid beta 40	7.636
Imbimbo et al. (2007)	CHF5074	61	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	22
									Amyloid beta 42	26
									Cellular infiltrates	16
									Plaque area	16
Jankowsky et al. (2005)	Environmental Enrichment	N/A		N/A	F	APP	<168.1	>168 and <336.1	Acquisition	16
									Amyloid beta 40	17
									Amyloid beta 42	17
									Probe	16
									RAWM	16
	Environmental Enrichment	N/A		N/A	F	APPPS	<168.1	>168 and <336.1	Acquisition	16
									Amyloid beta 40	19
									Amyloid beta 42	19
									Plaque area	19
									Probe	16
									RAWM	16
	Environmental Enrichment	N/A		N/A	F	PS1	<168.1	>168 and <336.1	Acquisition	16
									Probe	16
									RAWM	16
Kim et al. (2004)	A beta 1-42	N/A		INasal	U	APP	>168 and <336.1	>336 and <504.1	Plaque area	9
Kim et al. (2007b)	A beta 1-6	N/A		INasal	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Plaque area	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Kim et al. (2008b)	BMS-562492 (TACE INHIBITOR)	0	unknown	SubCut	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	TAPI-I	0		SubCut	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
Koldamova et al. (2005)	TO901317	50	mg/kd/day	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	20
									Amyloid beta 42	20
Lanz, Fici, & Merchant (2005)	Flurbiprofen	25	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	12.5
									Amyloid beta 42	12.5
	Flurbiprofen	50	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
	Flurbiprofen	100	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	12
									Amyloid beta 42	12
	Ibuprofen	50	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	20
									Amyloid beta 42	20
	Sulindac Sulfide	25	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	20
									Amyloid beta 42	20
	Sulindac Sulfide	50	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	20
									Amyloid beta 42	20
	Ibuprofen	50	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	20
									Amyloid beta 42	20
	Flurbiprofen	10	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	20
									Amyloid beta 42	20
	Flurbiprofen	25	mg/kg/day	Oral	F	APP	<168.1	<168.1	Amyloid beta 40	20

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	20
Lanz et al. (2008)	hIGF	500	ug/kg/day	SubCut	U	APP	>168 and <336.1	>168 and <336.1	TAU	13.5
	hIGF	50	ug/kg/day	SubCut	U	APP	>168 and <336.1	>168 and <336.1	TAU	13.5
Lavie et al. (2004)	EFRH	10	phage copies	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	7
									Amyloid beta 40	7
									Amyloid beta 42	7
	EFRH	150	Phage copies	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	9
									Amyloid beta 40	9
									Amyloid beta 42	9
	EFRH	300	phage copies	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	8
									Amyloid beta 40	8
									Amyloid beta 42	8
Le Corre et al. (2006)	K252a	100	mg/kg	Oral	F	Tau	>168 and <336.1	>168 and <336.1	TAU	58
Lee et al. (2006)	Antibody NAB61	62.5	µg	Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	17
									Amyloid beta 42	17
	Antibody NAB61	62.5	µg	Iperitoneal	U	APP	>504	>504	Amyloid beta 40	30
									Amyloid beta 42	30
	Antibody NAB61	62.5	µg	Iperitoneal	U	APP	>504	>504	Acquisition	30
									Probe	30
	Antibody NAB61	62.5	µg	iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	10
Levites et al. (2006a)	Antibody Ab2	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Antibody Ab5	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	Antibody ab9	N/A		Iperitoneal	F	APP	<168.1	<168.1	Amyloid beta 40	10.5
									Amyloid beta 42	10.5
									Plaque area	10.5
	Antibody Ab42.2	N/A		Iperitoneal	F	APP	<168.1	<168.1	Amyloid beta 40	10.5
									Amyloid beta 42	10.5
									Plaque area	10.5
	Antibody Ab40.1	N/A		Iperitoneal	F	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
	Antibody Ab40.1	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
	Antibody Ab42.2	N/A		Iperitoneal	F	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
	Antibody Ab42.2	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	8
									Amyloid beta 42	8
	Antibody ab9	N/A		Iperitoneal	F	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	8
									Amyloid beta 42	8
									Plaque area	8
	Antibody ab9	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
	Antibody ab9	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	8
	Antibody Ab3	N/A		Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
Ma et al. (2006)	Antibody anti-beta 1-15	N/A		intraventriclular	U	APP	>168 and <336.1	>168 and <336.1	Plaque area	13
Malm et al. (2007)	Pyrrolidine Dithiocarbamate	20	mg/kg/day	Oral	U	APPPS	>168 and <336.1	>336 and <504.1	Acquisition	28
									Amyloid beta 40	28
									Amyloid beta 42	28
									Cellular infiltrates	28
									Plaque area	28
									Probe	28
Marutle et al. (2007)	Phenserine	25	mg/kg/day	Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Cellular infiltrates	6
Matsuoka et al. (2008)	NAP	5	ul/day	INasal	B	3xTgAD	>168 and <336.1	>336 and <504.1	TAU	24
	NAP	5	ul/day	INasal	B	3xTgAD	>168 and <336.1	>504	Probe	22
									TAU	22
McLaurin et al. (2006)	Epi-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	<168.1	Acquisition	12
									Amyloid beta 40	15
									Amyloid beta 42	15
									Cellular infiltrates	15
									Plaque area	15
	Epi-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Acquisition	12
									Amyloid beta 40	15
									Amyloid beta 42	15
									Cellular infiltrates	15
									Plaque area	15

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Epi-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Acquisition	15
									Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	15
									Probe	15
	scyllo-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	<168.1	Acquisition	12
									Amyloid beta 40	15
									Amyloid beta 42	15
									Cellular infiltrates	15
									Plaque area	15
	scyllo-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Acquisition	12
									Amyloid beta 40	15
									Amyloid beta 42	15
									Neurodegeneration	20
									Plaque area	15
	scyllo-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Acquisition	15
									Amyloid beta 40	15
									Amyloid beta 42	15
									Cellular infiltrates	15
									Neurodegeneration	20
									Plaque area	15
									Probe	15
	scyllo-cyclohexanehexol	0.3	mg/kg/day	Oral	B	APP	<168.1	<168.1	Acquisition	10
									Plaque area	10.67
	scyllo-cyclohexanehexol	1	mg/kg/day	Oral	B	APP	<168.1	<168.1	Acquisition	10

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	10.67
	scyllo-cyclohexanehexol	3.3	mg/kg/day	Oral	B	APP	<168.1	<168.1	Acquisition	10
									Plaque area	10.67
	scyllo-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	<168.1	Acquisition	10
	scyllo-cyclohexanehexol	10	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 42	10.67
	scyllo-cyclohexanehexol	30	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 42	10.67
	scyllo-cyclohexanehexol	5	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 42	10.67
	scyllo-cyclohexanehexol	N/A		Oral	B	Tau	not known	not known	Cellular infiltrates	20
									Neurodegeneration	20
Movsesyan et al. (2008)	A beta 1-11	N/A		SubCut	U	3xTgAD	<168.1	>504	Acquisition	14
									Amyloid beta 40	14
									Amyloid beta 42	14
									Cellular infiltrates	14
									Plaque area	14
									Probe	14
									TAU	14
Oddo et al. (2005)	nicotine	490	ug/mL	Oral	U	3xTgAD	<168.1	<168.1	Amyloid beta 40	10
									Amyloid beta 42	10
									Neurodegeneration	10
									Plaque area	10
									TAU	10
Oddo et al. (2006a)	Antibody A11	N/A		iHippocampus	U	3xTgAD	>168 and <336.1	>336 and <504.1	Plaque area	8
									TAU	8

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
Parachikova, Nichol, & Cotman (2008)	Exercise	N/A		N/A	U	APP	>336 and <504.1	>336 and <504.1	Amyloid beta 40	6
									Amyloid beta 42	6
			day	N/A	U	APP	>336 and <504.1	>336 and <504.1	RAWM	12
Patel et al. (2005)	Caloric restriction	0.4	restriction	Oral	M	APPPS	<168.1	<168.1	Cellular infiltrates	8
									Plaque area	8
	Caloric restriction	0.4	reduction	Oral	M	APP	<168.1	<168.1	Plaque area	8
Pedersen et al. (2006)	Rosiglitazone	30	mg/kg	Oral	M	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	14
									Amyloid beta 42	14
									RAWM	14
	Metyrapone	50	mg/kg	SubCut	M	APP	>168 and <336.1	>336 and <504.1	RAWM	14
Petrushina et al. (2008)	a beta 1-28	N/A		SubCut	B	APP	<168.1	>336 and <504.1	Cellular infiltrates	13
									Plaque area	13
Pugh et al. (2007)	DSP-4	5	mg/kg	Iperitoneal	M	APPPS	<168.1	>168 and <336.1	Fear conditioning	12
									Plaque area	12
	DSP-4	5	mg/kg	Iperitoneal	M	APPPS	<168.1	>168 and <336.1	Fear conditioning	12
									Plaque area	12
Qu et al. (2006)	A beta 1-42	N/A		SubCut	F	APPPS	<168.1	>336 and <504.1	Amyloid beta 42	8
									Plaque area	8
Quinn et al. (2007)	Lipoic acid	0.1	% of diet	Oral	F	APP	>168 and <336.1	>336 and <504.1	Acquisition	15
									Amyloid beta 40	15
									Amyloid beta 42	15
									Fear conditioning	15
									Plaque area	15

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Probe	15
Rakover, Arbel, & Solomon (2007)	Antibody BBS1	2	mg/kg	Iperitoneal	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	8.5
									Amyloid beta 42	8.5
									Cellular infiltrates	8.5
									NORT	8.5
									Plaque area	8.5
	Antibody BBS1	16	mg/kg	Iperitoneal	F	APP	<168.1	>168 and <336.1	Amyloid beta 40	10.5
									Amyloid beta 42	10.5
									Cellular infiltrates	10.5
									NORT	10.5
									Plaque area	10.5
Rezai-Zadeh et al. (2008)	epigallocatechin-3-gallate	50	mg/kg	Oral	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	20
									Amyloid beta 42	20
									Plaque area	10
	epigallocatechin-3-gallate	20	mg/kg	Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	RAWM	10
	epigallocatechin-3-gallate	50	mg/kg	Oral	F	APP	>168 and <336.1	>336 and <504.1	RAWM	10
Rockenstein et al. (2006)	Cerebrolysin	5	ml/kg	Iperitoneal	U	APP	<168.1	>168 and <336.1	Acquisition	24
									Neurodegeneration	24
									Plaque area	24
Rockenstein et al. (2007a)	Cerebrolysin	5	ml/kg	Iperitoneal	U	APP	<168.1	<168.1	Cellular infiltrates	12
									Neurodegeneration	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	12
	Cerebrolysin	5	ml/kg	Iperitoneal	U	APP	<168.1	<168.1	Cellular infiltrates	12
									Neurodegeneration	12
									Plaque area	12
Rosario et al. (2006)	Testosterone	10	mg	SubCut	M	3xTgAD	<168.1	>168 and <336.1	Plaque area	12
									T/Y maze	12
Sadowski et al. (2006)	Amyloid beta-12-28P	1	mg	Iperitoneal	F	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	22
									Amyloid beta 42	22
									Plaque area	22
									RAWM	22
	Amyloid beta-12-28P	1	mg	Iperitoneal	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	22
									Amyloid beta 42	22
									Plaque area	22
	Amyloid beta-12-28P	1	mg	Iperitoneal	F	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	22
Schilling et al. (2008)	PBD150	7.2	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Acquisition	10.5
									Amyloid beta 40	16
									Amyloid beta 42	16
									Probe	14
	PBD150	7.2	mg/g	Oral	B	APP	<168.1	>168 and <336.1	Plaque area	8
	PBD150	2.4	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 40	12
									Amyloid beta 42	12
	PBD150	7.2	mg/kg/day	Oral	B	APP	<168.1	>168 and <336.1	Amyloid beta 40	12
									Amyloid beta 42	12
	PBD150	2.4	mg/kg/day	Oral	B	APP	<168.1	>336 and <504.1	Amyloid beta 40	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Amyloid beta 42	12
									Fear conditioning	7.5
									Plaque area	6
	PBD150	7.2	mg/kg/day	Oral	B	APP	<168.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Fear conditioning	7.5
									Plaque area	6
	PBD150	2.4	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Fear conditioning	6
	PBD150	7.2	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	12
									Amyloid beta 42	12
									Fear conditioning	6
	PBD150	2.4	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Plaque area	6
	PBD150	7.2	mg/kg/day	Oral	B	APP	>168 and <336.1	>336 and <504.1	Plaque area	6
Seabrook et al. (2006a)	Minocycline	55	mg/kg/day	Oral	U	APP	<168.1	>168 and <336.1	Acquisition	12
									Amyloid beta 40	12
									Amyloid beta 42	12
									Cellular infiltrates	12
									Plaque area	12
	Minocycline	55	mg/kg/day	Oral	U	APP	>168 and <336.1	>336 and <504.1	Acquisition	12
									Amyloid beta 40	12
									Amyloid beta 42	12
									Cellular infiltrates	12

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Plaque area	12
Shim et al. (2007)	Lithium	60	mg/kg/day	Iperitoneal	B	Tau	>504	>504	TAU	9
	Lithium	300	mg/kg/day	Iperitoneal	B	Tau	>504	>504	TAU	9
Shim et al. (2008)	nicotine	5	mg/kg/day	Oral	B	APP	>168 and <336.1	>504	Acquisition	20
									Probe	20
	nicotine	30	mg/kg/day	Oral	B	APP	>168 and <336.1	>504	Acquisition	20
									Probe	20
	nicotine	180	mg/kg/day	Oral	B	APP	>168 and <336.1	>504	Acquisition	20
									Probe	20
Singer et al. (2005)	Lenti-siBACE1-6	0	mg/kg/day	iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Acquisition	10
									Probe	10
	Lenti-siBACE1-6	0	mg/kg/day	iHippocampus	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 42	16
									Plaque area	16
Sung et al. (2004)	Indomethacin	N/A		Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	12
	Nimesulide	N/A		Oral	B	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	15
									Amyloid beta 42	15
									Plaque area	12
Trinchese et al. (2008)	BDA-410	30	mg/kg	Iperitoneal	U	APPPS	<168.1	>168 and <336.1	Fear conditioning	23
									RAWM	23
				Oral	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	8.5
									Amyloid beta 42	8.5
	BDA-410	30	mg/kg	Oral	U	APPPS	>168 and <336.1	>168 and <336.1	Fear conditioning	15

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									RAWM	15
	e64	6.4	mg/kg	Iperitoneal	U	APPPS	<168.1	>168 and <336.1	RAWM	20
				Oral	U	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	7.5
									Amyloid beta 42	7.5
Tucker et al. (2006)	N-acetyl cystine	5	g/l	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
	paroxetine	250	ng/mouse	Oral	U	APP	<168.1	<168.1	Amyloid beta 40	7.333
									Amyloid beta 42	7.333
	erythromycin	N/A		Oral	U	APP	<168.1	<168.1	Amyloid beta 40	9.333
									Amyloid beta 42	9.333
Tucker, Borchelt, & Troncoso (2008)	Antibody 6E10	2	µg	icerebral	B	APPPS	>168 and <336.1	>336 and <504.1	Plaque area	10
	Antibody 6E10	5	µg	icerebral	B	APPPS	>336 and <504.1	>336 and <504.1	Plaque area	12
	Antibody 6E10	5	µg	icerebral	B	APP	<168.1	>168 and <336.1	Plaque area	8
	antibody Ib3	5	µg	icerebral	B	APP	<168.1	>168 and <336.1	Plaque area	8
	Antibody 7b6	5	µg	icerebral	B	APP	<168.1	>168 and <336.1	Plaque area	8
Wang et al. (2007)	Valsartan	10	mg/kg/day	Oral	F	APP	<168.1	>168 and <336.1	Acquisition	10.5
									Amyloid beta 40	10.5
									Amyloid beta 42	10.5
	Valsartan	40	mg/kg/day	Oral	F	APP	<168.1	>168 and <336.1	Acquisition	10.5
									Amyloid beta 40	10.5
									Amyloid beta 42	10.5
	Valsartan	10	mg/kg/day	Oral	F	APP	<168.1	>168 and <336.1	Acquisition	10.5
									Probe	10.5

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
	Valsartan	40	mg/kg/day	Oral	F	APP	<168.1	>168 and <336.1	Acquisition	10.5
									Probe	10.5
Wilcock et al. (2007)	NCX-2216	187	ppm	Oral	U	APPPS	>168 and <336.1	>504	Plaque area	22
	A beta 1-42	N/A		SubCut	U	APPPS	>168 and <336.1	>504	Plaque area	19
Yamamoto et al. (2005)	3F1 (FAB fragment)	N/A		Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6
									Amyloid beta 42	6
	4396C (FAB fragments)	N/A		Iperitoneal	U	APP	>168 and <336.1	>168 and <336.1	Amyloid beta 40	6
									Amyloid beta 42	6
	4396C (FAB fragments)	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	9
									Amyloid beta 42	9
									Plaque area	9
	4396C (FAB fragments)	N/A		Iperitoneal	U	APP	>168 and <336.1	>336 and <504.1	Amyloid beta 40	9
									Amyloid beta 42	9
Zamora et al. (2006)	a beta 1-9	N/A		intramuscular	B	APPPS	<168.1	>168 and <336.1	Amyloid beta 40	11
									Amyloid beta 42	11
									Cellular infiltrates	10
									Plaque area	10
Zhang et al. (2006)	TSG	120	umol/kg/d	Oral	B	APP	<168.1	>168 and <336.1	NORT	24
									Probe	24
	TSG	240	umol/kg/d	Oral	B	APP	<168.1	>168 and <336.1	NORT	24
									Probe	24
	TSG	120	umol/kg/d	Oral	B	APP	>168 and <336.1	>336 and <504.1	NORT	24
									Probe	24
	TSG	240	umol/kg/d	Oral	B	APP	>168 and <336.1	>336 and <504.1	NORT	24

Author and (Year)	Intervention	Dose	Unit	Route of Drug Delivery	Sex	Transgenic Model Group	Age at administration (days)	Age at assessment (days)	Outcome measure	N
									Probe	24
Zou et al. (2008)	A beta 1-15	N/A		INasal	U	APP	>168 and <336.1	>504	Acquisition	9
									Amyloid beta 42	9
									Plaque area	9
									Probe	9
	A beta 1-42	N/A		INasal	U	APP	>168 and <336.1	>504	Acquisition	9
									Amyloid beta 42	9
									Plaque area	9
									Probe	9
Cao & et al (2009)	T cells	150000	cells	Unknown	U	APPPS	>168 and <336.1	>336 and <504.1	Amyloid beta 40	10
									Amyloid beta 42	10
									Cellular infiltrates	10
									RAWM	18

Appendix III: Table explains experiments included in analyses conducted. For each publications are listed by author and year, intervention, dose, dose units, route of administration, sex (where U, unknown, M, male, F, female, and B, both), age at intervention administration (days), age at outcome assessment (days), outcome measure reported and number of animals used (N). Novel object recognition task (NORT), Radial arm water maze (RAWM)

Appendix IV: Notes from working in the Morris laboratory

Mice were handled extremely carefully and there were specific efforts to reduce both noise and distress. The task I had to do was to announce which mouse had to be assessed (identified by a hole in specific ear/coat colour), start the operating system by clicking "reference" on the specific mouse for a specific training trial. Vassilis would then start the experiment by pushing the button as the mice enter the pool. The software dictated the direction the mouse should enter the pool and where the platform should be positioned. When planning the experiments for the acquisition phase careful consideration was given as to whether mice had to turn "right" or "left" to avoid the mice learning where the platform was from a memory of specific movements. The system would take 0.1 seconds away from the measured time as an approximate response time from experimenters.

The mice were inserted into the pool facing the outside wall and Vassilis was often in the room at the same time as the mice began their search for the platform. Interestingly, he alternates the way he leaves the room each time to try to reduce the influence he may have on mouse behaviour. No noise was allowed when the mice were searching for the platform in case this influences behaviour. At the start of the specific experiment I was working on, the mice were trained to find the visible platform and were in the maze for up to 90

seconds. Upon completion of finding the platform, mice would remain there for 30 seconds and in the case that they did not find the platform mice would be placed on it for 30 seconds. It's an interesting point that knowing where the platform is doesn't show the mouse how to get there- I rely on the mouse processing the surrounding environment in order to find the platform on the next trial.

It was quite remarkable to note that some of the mice didn't seem interested in finding the platform, even after multiple trials and although these mice would be included for the visible analysis of the MWM they would not be taken further in the experimental setup. It is unclear exactly why individual mice behave in this way as it could be that they do not understand the task set or conversely that they do understand the task set but lack the motivation to complete it.

The next stage of the experiment was the acquisition phase where the mice were trained for 6 trials a day for a minimum of 3 days and a maximum of 10 days, stopping on the day that they reached the criterion, which is average latency of <20 seconds for the 6 trials of the day. There was one probe trial 10 min after that, another one 24 h later (both using the Atlantis platform) and a final one 7 d later, with no platform at all. Each time the mice reached the criterion (<20 seconds, which was quite stringent) they were given a probe

trial using the Atlantis platform. The advantage of using the Atlantis platform is that it rises up at the end of the probe phase test and thus reduces the confusion for the mouse. Although time in target quadrant was being used for statistical assessment it was quite clear that different mice used different strategies to find the platform. Some mice would use spirals around the pool, whereas others would take relatively straight lines around the pool. Some mice appeared to understand the visible platform task extremely well but a number could not locate the platform in these 90 second trials.

When mice left the pool they were put under a hot lamp to warm up before being put back into cages- and tubes for running around in with water/food were present at all times. Mice were given an active or control drug once per week.

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Chapter 1

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